

HAEMOGLOBIN LEVELS IN PREGNANCY  
AND THE PUERPERIUM.

A Clinical Study of 104 Cases  
with Critical Survey of the Literature.

by

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## INTRODUCTION.

Much attention is now rightly focussed upon ante-natal care, both from the aspect of the mother's health and the effects of impairment of her health in pregnancy, upon her offspring.

In a provincial town of the size of Hawick, where the work, shortly to be described, was carried out, there is afforded the opportunity to the individual doctor of following his own cases from the earliest days of pregnancy until discharge in the puerperium. The absence of public ante-natal clinics conducted by Public Health Officials, and the custom, which almost amounts to a tradition, even amongst the poorest classes, of having the attendance of the family doctor, ensures the continuity of supervision to the patient, where the individual doctor is willing to undertake this work.

This opportunity and the fact that it was considered possible to collect a sufficiently large number of cases in a reasonable time, largely determined the choice of the pregnant woman for a clinical study. Further, it was felt, but not confirmed by facts, that the type of patient met with here presented very few of the grosser complications of pregnancy, labour or the puerperium. A clinical study during these three phases of active sexual life would either confirm or confound this impression.

The/

The object of ante-natal care may justly be said to be preventive and this it achieves in two main ways (1) By education of the patient in correct physiological principles and habits during pregnancy. (2) By early discovery of any abnormality and its correction and treatment where possible. These two ways are not altogether exclusive since the first aims at preventing the onset of complications by correct hygiene.

Perhaps the most important aspect of ante-natal care is the instruction of the patient in correct diet. Certainly, the present investigation concerned with the blood state in pregnancy is most closely linked with this aspect of ante-natal care. To undertake a proper dietary survey of cases was at first thought to be a possibility, but it was soon seen that to make this investigation accurate would have involved work of a kind which it was quite impossible under the circumstances of general practice to undertake. At any rate the chief factors in regard to the diet of the pregnant woman have been thoroughly worked out and recorded many times and any study which would have been possible would not have afforded any fresh information. The idea of making a dietary survey was therefore abandoned and the blood state in pregnancy became the sole pre-occupation.

By studying the blood state in a series of women, an indirect investigation into the adequacy of the diet/

diet was being made, since it is obvious that the person in health is dependent entirely upon the diet for the supply of haematinic substances. Particularly is this the case with iron which is one of the minerals likely to be defective even in the diets of the non-pregnant.

It was realised that iron deficiency if it existed, or even if it did not exist to any degree in this series, was only one of many defects which could be made good by proper diet before and during pregnancy. Other minerals such as Calcium, Phosphorus and Iodine with the vitamins are no less important for the health of the mother and that of her offspring, but these did not lend themselves to such easy clinical study and therefore iron is the dietary constituent upon which interest has centred; since its lack is clearly reflected in the blood condition which is relatively simple to investigate.

Routine haemoglobin investigations during the ante-natal and post-natal periods were therefore undertaken and general instruction in regard to dietary and hygiene were given to each patient. Realising that any iron deficiency is best made good by the administration of inorganic iron, a series of cases were given iron and a further series were left untreated, except where obvious indications for its use arose, and so it was hoped to have some light thrown upon the problem of the iron needs of pregnancy. With this problem/



problem the main part of the work is concerned.

In a study of 104 consecutive cases, the incidence of certain abnormalities could also be recorded and particular attention was focussed upon anaemia in pregnancy. It was hoped that the study would reveal the incidence of anaemia in pregnancy in a community such as this, where the bulk of the patients belonged to the working middle-classes in which unemployment and poverty were not marked.

The object of this study may therefore be summarised by saying that it was hoped by a study of the blood condition in pregnancy and the puerperium to arrive at an understanding of the incidence of anaemia during this period of a woman's life. Further, by the administration of iron experimentally to certain groups of patients, to come to a better understanding of the role of iron therapy in pregnancy and the puerperium. As a secondary object the incidence of other abnormalities of pregnancy and the puerperium could be ascertained, particularly those likely to be influenced by or to exert an influence on the blood picture.

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METHOD.

During the period August 1940 to September 1941 it was possible to study 104 women during pregnancy and the puerperium. The majority were personal cases derived from general practice and these were followed from the first day of reporting in the ante-natal period until the termination of six weeks after delivery. The cases varied somewhat in regard to social status, but none could be classed as really poor; most were the wives of factory workers in steady employment and quite a number belonged to the professional classes. Some women were confined in their own homes and attended by qualified midwife and doctor, but the majority were delivered in a small maternity hospital in Hawick.

In those followed from the ante-natal period until the termination of the sixth post-partum week, it was possible to do frequent haemoglobin estimations. These estimations were done at least every four weeks in the ante-natal period and as labour drew nearer the haemoglobin readings were taken at more frequent intervals; especial attention being paid to the last four weeks of gestation when readings were obtained as often as practicable.

During the puerperium it was, at first, the custom/

custom to obtain haemoglobin readings at 3 or 6 hour intervals. This, however, did not seem to afford any particular advantage and thereafter daily estimations were taken until the haemoglobin showed signs of definite improvement. Thereafter the estimations were made on alternate days and sometimes less often until discharge from hospital, usually between the 10th and 14th days of the puerperium. Haemoglobin readings during the 3rd - 6th weeks were less frequent and were taken as the opportunity arose. The final readings of the haemoglobin was taken as near as possible to the completion of the 6th week after delivery.

As indicated, a small number of cases were derived from other sources. These were cases admitted to the hospital in labour or shortly before, and had been attended by other doctors before admission. From these cases it was possible to obtain a haemoglobin reading for the termination of pregnancy and they were followed during the puerperium as indicated above. None of these cases had received any pre-natal iron therapy.

The Haemoglobinometer used was the Sahli with a permanent standard of coloured glass. The capillary blood was obtained by needle puncture of the dorsal aspect of the terminal phalanx of the thumb. Due care was observed to avoid congestion of the part. The blood was drawn into the pipette up to the 20 cmm. mark/



mark and then expelled into N/10 HCl. which filled the dilution tube up to the mark 10. A rapid method of reading the percentage haemoglobin was required. The HCl was allowed to act upon the blood for 45-60 seconds before dilution with water and estimation of the haemoglobin by comparison with the permanent standard. It was found that there was no difficulty in obtaining a definite colour match by this method.

It was fully realised that the time allowed did not permit of the complete action of the acid on the blood. Myers<sup>71</sup> in his "Practical Chemical Analysis of the Blood" (1924) allows two hours for the change to acid haematin to take place. This is clearly impracticable where several estimations are requiring to be done in a limited time. Higher readings - depending upon the time of interaction of blood and HCl - are obtained by this more accurate method, but the shorter method employed is recognised for clinical work and can be relied upon if the technique is standardised and the instrument calibrated for this technique.

The Sahli Haemoglobinometer used was the same one throughout. Individual error was eliminated by all the results being obtained personally. The instrument was standardised for this technique at 16 Gms Hgb. per 100 ccs. of Whole Blood = 100%.

The haemoglobin content of the foetal blood was estimated/

estimated in some cases from the cord blood or capillary blood from heel prick, but in these cases it was found that a longer period was required for the interaction of blood and acid in order to obtain an accurate colourimetric estimation of the haemoglobin. The percentages given for foetal haemoglobin are therefore not comparable with these obtained from the mother, but are comparable one with another on a percentage basis.

Each patient on reporting for examination in pregnancy had the haemoglobin estimated. Alternate cases were given iron therapy for the remainder of pregnancy, in the form of three Fersolate tablets daily, while the others received no iron therapy unless definite signs of anaemia developed. There were a few cases mildly anaemic who, for experimental reasons, were not given iron. No real signs of intolerance to iron developed, although some complained at first of mild gastro-intestinal upset. With persuasion, these patients continued taking the iron with a disappearance of the symptoms of which they had complained. Some patients missed occasional doses of iron, but none defaulted to such an extent as to affect the results of iron therapy, as measured quantitatively.

The date of delivery was taken as the end of the 40th week of gestation, unless there were definite reasons for believing that prematurity or postmaturity existed/

existed. If such existed due allowance was made in any calculations affected thereby.

Immediately after delivery the patients were again divided into two groups - Iron treated as before delivery and a control group untreated. Iron administration was continued for six weeks after delivery. Any in the untreated group who showed anaemia in the puerperium were given iron. Usually the anaemia manifested itself early in the puerperium, so that, for the most part all these anaemic cases were iron treated during the 6 weeks from the time of labour.

At the end of the investigation the cases were grouped according to any abnormalities which occurred in the ante or post-natal periods and which were likely to have an influence upon the blood condition of the patient. The groups will be discussed later but are as follows:-

1. Normal Cases. Those showing no anaemia and no complication of pregnancy or the puerperium.

2. Ante-Natal Anaemia. Those showing a hypochromic anaemia with no complicating or apparently causal factor.

3. Excessive Blood Loss at Labour. All of these could not be said to have a true post-partum haemorrhage. Where the loss appeared to be more than average the cases were placed in this group.

4. Ante-Partum Sepsis. Those who showed definite signs of a septic focus. The cases in this investigation all had Pyelitis.



5. Post-Partum Sepsis (a) Pyelitis (b) Mastitis  
(c) Uterine and other Pelvic Inflammations.  
6. Toxaemias of Pregnancy.
-

### NORMAL HAEMOGLOBIN STANDARDS.

Before embarking upon any discussion or consideration of Haemoglobin levels it is necessary to establish some normal standards by which the results can be gauged.

In the first place let us consider the normal standards of haemoglobin for the non-pregnant state. An attempt will be made to establish a fair average haemoglobin for this community, but before doing so it will be helpful to consider the relevant literature on this subject.

Davidson and his co-workers<sup>18</sup> (1935) in establishing a normal for males and females remarked that the literature afforded little help, as levels seemed to vary from one country to another. The level adopted by most workers in this country is that established by Price Jones<sup>79</sup> (1931) and his investigations on 100 normal healthy young adults of both sexes. Age in the groups studied was not a factor. Menstruation was not considered a factor of any importance and this function was not investigated in the 100 women examined. As all lived at the same altitude, this also did not affect the results. Sex was a factor of importance as the average results show, 105% for men and 98% for women. The Standard used was 100% = 18.5 ccs. per cent O<sub>2</sub> Capacity (Haldane).

Mackay/

63

Mackay (1935) adopts this standard in her investigations upon London Women of the poorer class and Davidson et al<sup>18</sup> (1935) used the Price Jones standards in their investigations in Aberdeen. They make an allowance of <sup>+</sup> 10% in order to establish a range of normality.

80

Ramsay et al<sup>80</sup> (1938), working in this country, adopt a slightly lower standard of normality. They fix 80% (Haldane) as the lower limit of normal and as they are working with a Dare Haemoglobinometer (100% = 16 Gms per 100 ccs) the percentage adopted by them is 70% (11.2 Gms per 100 ccs) for women of child-bearing age. This is approximately 1 Gm per 100 ccs lower than the figure adopted by Davidson.

Turning to workers in other countries, we find that amongst the American workers there is also variation.

75

Osgood and Haskins (1927) investigated the haemoglobin and other levels in 100 normal young women in America and found that the haemoglobin averaged 13.69 Gms per 100 ccs. This was the most frequently occurring figure and 90% lay between 12 and 15.5 Gm per 100 ccs. The lowest was 10.98 Gms which corresponds fairly well with the figures given by Ramsay et al. The highest was 16.49 Gms so that all of the 10% did not fall short of 12 Gms. per 100 ccs. If we assume that those below 12 Gms. (less than 10%) had a mild anaemia then the figure of 12 Gms. is very similar to that adopted by Davidson et al (88% Haldane or 12.14 Gms per 100 ccs. blood).



Bethell<sup>5</sup> (1936) using a modified Sahli Haemoglobinometer (100% = 15.8 Gm per 100 ccs) found an average haemoglobin in 50 normal women of 87.5% - ranging from 78% - 97%. Converting the average into Gms. per 100 ccs, we obtain 13.8 Gms or the equivalent of 100% Haldane. Allowing  $\pm$  10% the lower level of normal in this case is only slightly higher than the estimates accepted by Davidson et al.

Watson<sup>90</sup> (1938) who used a Sahli Haemoglobinometer calibrated so that 100% = 14 Gms per 100 ccs. found that 55% was the lower limit of normality in pregnancy. Adding 10% to compensate for the dilution of the blood in pregnancy we have a lower limit of normal of 65% which is equal to 9.1 Gm. per 100 ccs. This is considerably below any of the standards already mentioned.

The following table sets out these results in a way in which they are more readily compared.

See TABLE I.

It will be seen that there is no absolute figure which one can adopt as normal, although the evidence of the figures quoted, would incline one to accept a figure in the region of 12 Gms per 100 ccs. of whole blood, as a fair estimate of normality.

In view of the disparity of results, an attempt has been made to establish a normal average haemoglobin for healthy non-pregnant women of child-bearing age/

Author.	Normal Range.	Method.	Calculated Lower Limit of Normality (Gm. per 100 cc.).
1. Price Jones	98% (Av.)	Haldane	-
2. Davidsonetal	+ 98%	ditto	12.14
3. Mackay	Price Jones	Standard	-
4. Ramsayetal	-	Dare	11.20
5. Osgood & Haskins	10.98 - 16.49 Gm. %	-	10.98 or 12.00
6. Bethell	78% - 97%	Sahl1 (modified)	12.20
7. Watson	-	Sahl1	9.10

TABLE I.

age in this community. The Sahli haemoglobinometer used was the same as in the cases of pregnancy. No regard was paid to diurnal variation (Price Jones<sup>79</sup> (1931)) and the estimations were scattered over different periods of the year. There were 40 nulliparous women and 23 parous women. The number of pregnancies in the latter group appeared to have no effect on the haemoglobin levels.

The Results were as follows:-

See TABLE II.

It will be seen that the average results for the two groups vary but little. The average of 98% Haldane adopted by Price Jones corresponds to 13.52 Gms Haemoglobin per 100 ccs. which is rather lower than the findings in this smaller series presented here. Some workers have thought that the average normal figure for haemoglobin should be higher than 13.52 Gm. and probably in the region of 14 Gms. per 100 ccs. At any rate the results here presented seem to bear out the standards already adopted.

Later the adoption of a lower normal standard for pregnancy will be discussed. Using the standard established here and making, due allowance for the blood changes of pregnancy, it will be shown that the calculated result differs only slightly, if at all, from that proved by experiment to be correct.



	Nulliparae	Multiparae	Both Groups
No. of Results	40	23	63
Range	78% - 100%	78% - 105%	78% - 105%
Average	85.9% = 13.74 Gms.	87.4% = 13.98 Gms.	86.5% = 13.84 Gms.

TABLE II.

NORMAL HAEMOGLOBIN STANDARDS IN PREGNANCY.

A normal standard having been established for the non-pregnant state, we must now endeavour to establish a normal standard for the pregnant woman. In so doing we shall be anticipating to some extent the fuller discussion on the blood changes of pregnancy and the puerperium, but it seems convenient at this state to try and establish a normal haemoglobin standard. First of all the relevant literature will be searched and secondly one's own estimate of a normal standard will be given.

Without entering into a discussion here on the Hydraemia of Pregnancy it will be stated, that it is mainly on account of the existence of a dilution of the blood in pregnancy that it becomes necessary to establish fresh standards for this condition.

A survey of the literature on the blood changes in pregnancy at once reveals the lack of any definite standard below which anaemia may be said to exist. Doubtless there are many difficulties to be overcome and it is impossible perhaps to make any hard and fast rule, particularly as the degree of hydraemia may not be a constant feature. Some authors have allowed of a 10% fall in haemoglobin to be accounted for by hydraemia but this cannot be applied universally. Even allowing a 10% fall for hydraemia we find that the figures of different authors vary in regard to their/

Author.	No. of Cases.	Period of Gestation.				Haemoglobin % age 4 Gms/100cc. Irrespective of Period of Gestation.	Method of Estimating Haemoglobin.	Lowest Normal Haemoglobin Level.	Remarks.
		First Trimester. Haemoglobin % age 4 Gms/100cc.	Red Blood Cells per cmm.	Second Trimester. Haemoglobin % age 4 Gms/100cc.	Red Blood Cells per cmm.	Third Trimester. Haemoglobin % age 4 Gms/100cc.			
Lyon. (32)	1929. 200.					75.3% = 11.89 gms.	Sahli.		
Galloway. (30)	1929. 382.	73% = 11.5 gms. $4.05 \times 10^6$		69% = 10.9 gms. $3.94 \times 10^6$		66% = 10.42 gms. $3.87 \times 10^6$	Sahli.	65% = 10.27 gm.	48% patients primigravidae.
Bland et al. (43)	1930. 300.						Dale.	75% = 10.35 gm.	
Moore. (85)	1930. 300.								* Calculated from Haldane's scale. 45% primigravidae.
Mackay. (21)	1931. 109.						Haldane.		Poor class mothers in London.
Strauss. (31)	1933. 12.					76% = 11.85 gms. #	Sahli.		* Full term in only 12 non-anaemic patients.
Davis & Walker. (73)	1934. 189.						Hayden-Hauser.	70%.	64% anaemic on this standard.
Dieckmann & Wegner. (41)	1934.							10 gms.	
Davidson. (26)	1935. 819.						Haldane.		49.5% < 80%.
Mackay. (22)	1935. 109.						Haldane.		
McGeorge. (42)	1935. 100.					83% - 87% 11.5 - 12.0	Helliger.		Percentages in Haldane equivalents. 83% at 29-34 wks. 87% at full term.
Inwing. (75)	1935. 60.	67% = 10.58 gms. $3.99-3.94 \times 10^6$					Sahli.		
Bell. (38)	1936. 66.						Sahli.	70% = 11.06 gms.	Examination during last Trimester. 70% of cases below 70%.
Goodal & Gottlieb. (12)	1936. 200.	80% = 11.2 gms. $4.3 \times 10^6$		75% = 10.59. $4.1 \times 10^6$		65% = 9.1 gms. $3.7 \times 10^6$			
Stewart & Gottlieb. (13)	1936. 75.							75% = 10.5 gms.	
Adair et al. (57)	1936. 8,005.					11.56 g. $3.77 \times 10^6$	Newcomer.	10.16 Gms.	11.6% Patients anaemic on this standard.
Corrigan & Strauss. (40)	1936. 200.						Sahli.		Haemoglobin estimation at patient's 1st visit.
Fullerton. (53)	1936. 376.					74% = 11.54 gms. 74.6% - 79.2% 10.29 gm - 10.92 gms	Haldane.		Haemoglobin level varies with age of group.
Fullerton. (53A)	1936. 1166.	83.3% = 11.49 gms.				* 74.3% - 76.5% 10.25 gms - 10.55 gms.	Haldane.		* Lower reading 37th week. Higher at 39th week.
Smallwood. (54).	1936. 106.							* 70% ? = 9.67	* No mention of Hgb meter. Probably Haldane.
Boycott. (39)	1936. 222.			96.5% = 13.17		* 89.4% = 12.33 gms.	Haldane.	* 80% = 11.04 gms	* Admitted to be high. Standard in pregnancy not mentioned.
Oberst & Plass. (51)	1936. 20.							11.69 gms.	From 152 selected normal cases showing no anaemia.
Reid & McIntosh. (56)	1937. 1108.								10 primigravidae.
Ramsay et al. (58)	1938. 95.					77.8 = 12 gms.	Haldane.	70% = 9.67 gms.	10% of patients under 70%
Watson. (101)	1938. 500.						Dale.		
McCance. (92)	1938. 107.						Sahli. (100% = 14.5m)	55% = 7.7 gms.	Only 5% anaemic according to this standard.
Linder & Massey. (19)	1939. 213.						Haldane.		* This figure is the average obtained from 16 patients forming the group with lowest income. Other groups higher.
Gottlieb & Stream. (7)	1939. 275.	80% = 11.2 gms.		75% = 10.5 gms.		65% = 9.1 gms.			
Labate. (15)	1939. 881.								
Labate. (14)	1940. 11.					9.6 - 10.16 gms. $3.47 \times 10^6$ $3.70 \times 10^6$	O <sub>2</sub> Capacity	80% = 11.6 gms.	Haemoglobin figure probably high as author talks of mild anaemia and hydraemia as being the same.
Estimated Normals.		11.20 = 11.50 gms.		10.50 - 10.90 gms.		10.50 - 10.90 gms.		10.00 Gms.	Lower figures for Hgb and R.B.Cs. taken at 38th week. Higher figures for 40th week.



individual case variation (and this must be admitted even in the simple haemoglobin estimation) and maintain that only individual study gave any clear idea of what really happened to the blood in pregnancy.

Admitting that each case must be judged on its merits, yet in order to establish some sort of standard for any particular factor the method of averaging as many results as possible is the method least prone to error, since any sudden individual variation is excluded. This point was stressed by Irving<sup>44</sup>(1935) many of whose cases showed sudden changes in haemoglobin unaccounted for except on the basis of rapid change in blood volume. Having said all this it must be admitted that there is a definite fall in haemoglobin as pregnancy proceeds, presumably due to the increasing foetal demands which are greatest in the last three months (Whitby<sup>91</sup>(1932) and Castle and Strauss<sup>13</sup>(1932)). The results tabulated for the trimesters of pregnancy shows this, as does the work of Davies and Shelley<sup>22</sup>(1934) (Not tabulated) who showed a fall in haemoglobin and red blood cells in the last trimester of 8% on an average of 57 normal pregnancies.

Is it possible from the results recorded of the haemoglobin in the three trimesters to come to any figure for the haemoglobin which might be considered normal for each period?

Since/

Since each author uses a method which may be different from another, the expression of haemoglobin as a percentage is not an accurate method. The percentage results therefore have been converted into Gms. of Haemoglobin per 100 ccs. of Whole Blood, using the standards given by the various authors e.g. Haldane 100% = 13.8 Gms per 100 ccs. In some instances the Sahli 100% varies, but where no mention is made of the Standard in an article, the Sahli 100% has been taken to represent 15.8 Gm. per 100 ccs. Considered on the basis of Gms. per 100 ccs. the haemoglobin values given are strictly comparable.

The results given for haemoglobin in the first trimester vary between 10.58 Gm. (Irving<sup>44</sup> (1935)) and 11.50 Gms. Only the lowest result (10.58 Gms.) differs appreciably from the others which only vary slightly (11.20 Gm. - 11.50 Gms). The figure of 11.20 - 11.50 Gms. may be taken as a fair average for the first trimester, although the figure of 10.58 Gms could not be considered to be below the normal for any one case, as will be seen later.

The results of Boycott<sup>8</sup> (1936) are high for each trimester since they have been calculated from results obtained from 152 normal, non-anaemic cases. They can therefore be excluded.

The results tabulated for the second trimester of pregnancy correspond closely and vary from 10.50 Gms. to 10.90 Gms. A definite drop therefore is noted amounting at most to 1 Gm. haemoglobin per 100 ccs.

When we consider the last trimester we see that there is at times a wide variation in the results of different authors. This is probably explained to some extent by the fact that in the latter weeks of pregnancy there is in some cases a definite rise in haemoglobin (McGeorge<sup>61</sup>(1935), Fullerton<sup>33</sup>(1936) and Labate<sup>51</sup>(1940)). This rise has not been found universally and will be considered more fully in relation to blood volume under Hydraemia. For the present it is sufficient to note that the average haemoglobin value for the third trimester approximates to that found in the second three months, probably being somewhat lower at the start of this period and tending to rise in the last two or three weeks.

The answer to the question must therefore be in the affirmative. The results given enabling us to have some standard for comparison.

As was previously mentioned there are many authors whose work has only enabled them to give a mean average haemoglobin for the whole of pregnancy. Usually the numbers have been large and the patients representing every stage of pregnancy. These facts give to the figures a value as a mean for the whole of pregnancy.

Looking at the figures more closely we find that four of them lie between 10.76 Gm. and 10.92 Gms. Of the other six results tabulated the result given by/



Mackay<sup>63</sup> (1935) is higher than the figure previously given by her in<sup>(62)</sup> 1931 when 109 mothers in London gave an average of 10.76 Gm. The 1935 series consisted of unmarried mothers in a hostel where probably the dietary standard was adequate. The results of Adair et al<sup>2</sup> (1936), and Corrigan and Strauss<sup>17</sup> (1936) appear high for this country, but the results of the latter may have been raised owing to the fact that the estimations were made at the first visit, many of which may have occurred in the first three months of gestation. The result of 11.69 Gm. given by Oberst and Plass<sup>73</sup> (1936) is derived from a very small series and therefore may lack the accuracy of the others so far as average results are concerned. The results of Linder and Massey<sup>53</sup> (1939) in Cape Town, appear high by all other standards. Even allowing that the readings of haemoglobin were obtained in the last trimester and assuming that a majority were taken at term and showed a rise in haemoglobin, the result of 12.4 Gms. is higher than any given in this country. The result given by McCance<sup>58</sup> (1938) falls below any of the others but it has to be remembered that this result is obtained from the patients in the lowest income group studied and that their haemoglobin was shown to be correspondingly reduced. An average of all his results would be nearer the results quoted first and agreeing so closely with each other.

We/

We may therefore take 10.76 Gms. - 10.92 Gms. as a range of normality for the whole of pregnancy.

In any large series of cases many individuals will fall short of the figures given for each trimester and the whole of pregnancy. Not all of these can be considered anaemic, however, since most show a reduction in red blood cells corresponding with the reduction in haemoglobin and are probably indicative of a greater increase in plasma volume, which will be fully discussed later. The results already given are not therefore minimum values of normality. It is necessary to try and establish this level as further discussion will be concerned with the incidence of the anaemia of pregnancy.

It is customary (Davidson et al.<sup>18</sup> (1935) to allow a range of  $\pm 10\%$  on the average normal. A reduction of 10% on the figures given for the whole of pregnancy would give the lower level of normal lying between 9.69 Gms. and 9.83 Gms. Studying the figures given in the table we shall see how closely these correspond to the figure just mentioned.

Out of the 11 results given 5 lie close together only varying from 10.00 to 10.50 Gms. Smallwood<sup>84</sup> (1936) and Reid and McIntosh<sup>81</sup> (1937) give a figure of 9.67 Gms. which is only slightly lower than the figure quoted. Of the other figures given, that quoted by Bethell<sup>5</sup> (1936) is probably high since he states that 70% /

70% of his cases are anaemic according to his standard of 11.06 Gms., which was obtained from patients in the last trimester. Boycott<sup>8</sup> (1936) gives a figure of 11.04 Gms. or 80% Hgb. which also appears to be rather high as his percentage of anaemia (22% below this standard at some time in pregnancy) is higher than that of most other workers. He also states that 80%<sup>Hgb.</sup> is the figure derived from the study of non-pregnant females and that the standard for pregnancy must be lower and varies in the literature. The remaining high figure of 11.60 Gms. given by Labate<sup>49</sup> (1939) is probably too high since the author in his article talks of the hydraemia of pregnancy as being a mild type of anaemia. In this case it is to be expected that the figure would be high. Lastly the remaining figure of 7.7 Gms. given by Watson<sup>90</sup> (1938) would appear to be low since it is not in agreement with any other figures and further, the author only reports an incidence of 5% of anaemia in pregnancy, which is considerably lower than any others in the series.

Thus once again we arrive at a figure from the study of the literature which may be said to lie between 10 Gms. and 10.50 Gms. This is not materially different from that calculated at the beginning of this section viz. 9.69 Gm. to 9.83 Gms. For practical purposes the lower level of haemoglobin for normal pregnant women may be taken as 10 Gms. per 100 ccs.

It/



It will be seen from the above discussion that the normal haemoglobin level in pregnancy can be estimated from the literature. The most accurate method appears to be to consider each trimester separately, although fallacy is apt to arise in considering the last trimester near term. But an average figure can be given to cover the whole of pregnancy and the lower limit of normal can be fixed about 10% below this average figure.

At this stage it will be instructive to consider the results obtained in the normal control groups studied.

At the outset it was necessary to adopt some arbitrary level below which anaemia might be said to exist, since it was intended to treat the anaemic cases with iron and to have two groups of non-anaemic normal women - the first group treated as the anaemic cases and the second group to act as a control group in pregnancy. The level first adopted was 70% (own Sahli) but the investigation had not gone far when it became clear that a very large number of apparently normal women, with no symptoms or signs of anaemia, were finding themselves in the iron treated group. It was then decided to adopt a lower standard of normality and 60% (Sahli) = 9.60 Gms per 100 ccs. was adopted. As the investigation proceeded and several women, who had received no iron, came to term it/

it was observed that the haemoglobin very often rose towards term, especially in the last two weeks. This was taken as an indication that the level of 60% was probably not too low since truly anaemic women would not be expected to show this spontaneous rise.

The figure of 60% (9.60 Gms Hgb.) was therefore adopted and it is interesting to compare this with the figures given in this section while discussing the literature. The lowest normal levels from the literature lay between 9.69 and 9.83 Gms. of haemoglobin per 100 ccs. of whole blood. This is not greatly different from the level adopted here. If we had adopted 10 Gms. per 100 ccs as a convenient and likely lower level of normality then this would have corresponded with a reading of 62.5% on the haemoglobinometer used. The difference between 62.5% and 60% in the instrument used is so small that there seemed no justification for altering the lower limit from 60% to 62.5%. 60% was therefore taken as an absolute lower limit of normal haemoglobin in pregnancy.

It is interesting to calculate the lower limit of normal from the recognised facts presented in the literature. Using the Haldane Haemoglobinometer 98% is the accepted average standard for women. 98% (Haldane) is equivalent to 84.5% (Sahli 16 Gm = 100%). Allowing the usual range of  $\pm 10\%$  we obtain a lower limit/

limit for normal non-pregnant women of 74.5%. The dilution of the blood in pregnancy is the factor which leads to a further reduction in the haemoglobin and this will be discussed fully later. However, we may anticipate this discussion, by stating that the amount of hydraemia may be a variable factor but that 15% reduction in the haemoglobin may on occasion be the result of hydraemia. Deducting this 15% we therefore find that we are again reduced to about 60% (Sahli) as the lower limit of normality in pregnant women. It is interesting to note that, using the normal figure given earlier for the non-pregnant state of women in Hawick, there is no appreciable difference in the calculated lower normal level in pregnancy, from that just given.

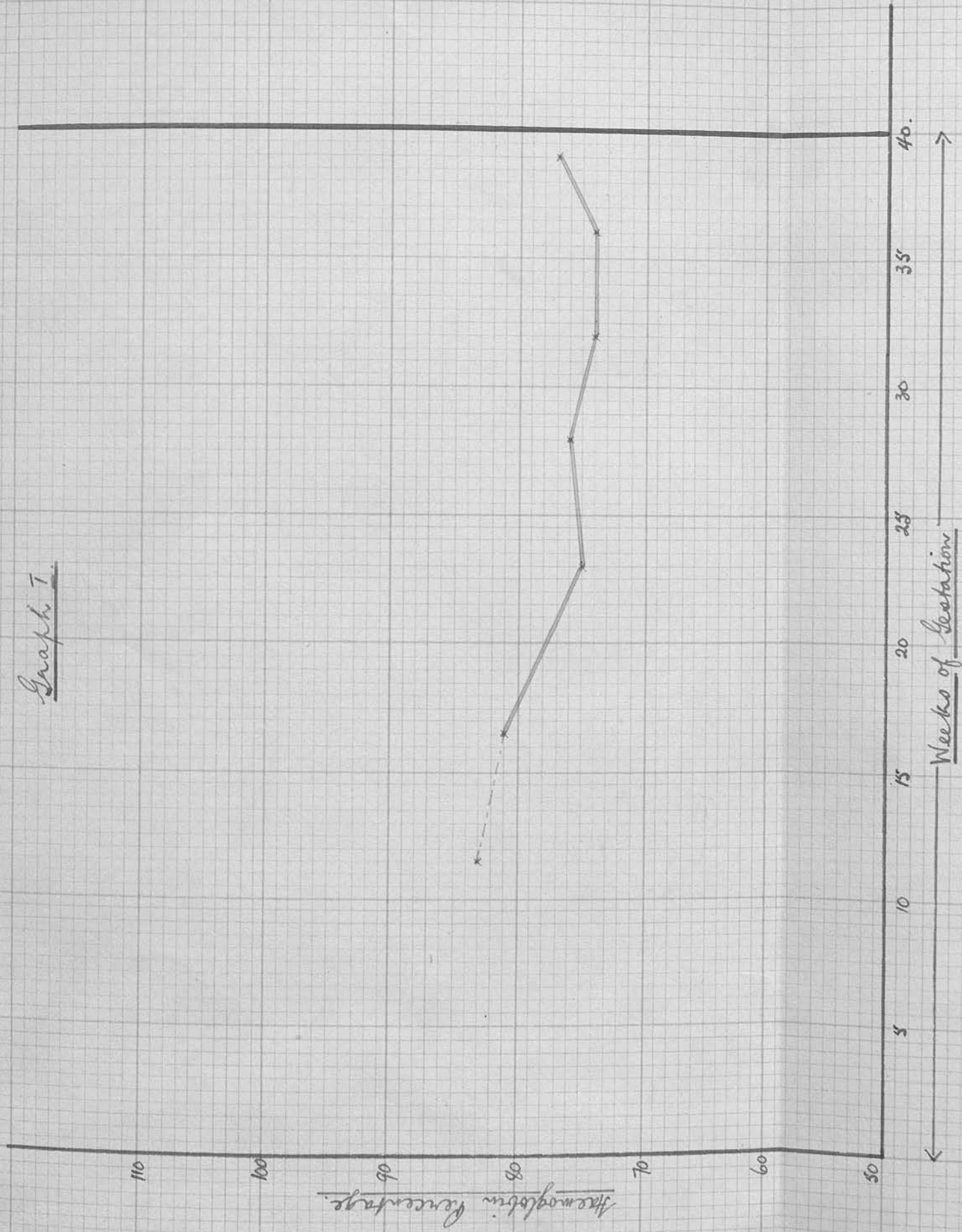
The results of the investigation of 40 normal control cases during pregnancy are now given and seem to justify the levels adopted above. Graph I is compiled from the average of numerous readings from the 40 cases at different stages in pregnancy. No case was seen before the 10th week of pregnancy.

The period 13-26 weeks was divided into two roughly equal periods (1) 13-19 inclusive and (2) 20-26 inclusive. This takes us to the end of the 2nd trimester of pregnancy. Thereafter the results were more numerous and since each patient was seen at least four-weekly for the remainder of pregnancy periods of four weeks were selected as in the Table IV. During the last/



25 a.

Graph I.



Weeks of Gestation	13 - 19	20 - 26	27 - 30	31 - 34	35 - 38	39 - 40
No. of results	25	36	29	31	43	59
Range %	65 - 95	67 - 91	67 - 85	60 - 89	63 - 87	60 - 96
Av. Hgb. %	81	75	76	74	74	77

Number of Cases from which results were obtained = 40.

TABLE IV.

last two weeks many cases were seen frequently in order to study the behaviour of the haemoglobin near term and therefore the last average applies to this period of a fortnight. Table IV is compiled from Graph I in order to facilitate reference to figures. The Graph enables us to follow the fall and rise of haemoglobin in pregnancy more easily.

See TABLE IV.

Regarding the behaviour of the haemoglobin level during pregnancy we agree with those who found a fall which showed itself in the second trimester. This fall seems to be maximal towards the end of the second trimester. It is maintained throughout most of the third trimester, but there is a definite attempt at a return to normal - in this series - during the last two weeks of pregnancy. This group of control cases will be further discussed and compared later with a group of Iron-treated cases, therefore, no further analysis will be attempted here. However, the results appear to be substantially in agreement with the deductions drawn from the study of the literature and the normal levels adopted seem to be justified.



## THE BLOOD CHANGES IN PREGNANCY AND THE PUERPERIUM.

### A. The Hydraemia of Pregnancy.

That there is some alteration in the blood in pregnancy tending towards a more watery state has been known since the observation of Nasse<sup>72</sup> (1876) and later of Zangemeister<sup>96</sup> (1903) who observed a lowering of the Specific Gravity of the blood of the pregnant woman. Zangemeister also noted that this lowering of the S.G. was the result of, and accompanied by, an increase in the water content and a diminution in the total solids (De Wesselow<sup>24</sup> (1922)) particularly the plasma proteins. This latter observation was confirmed by later workers (Landsberg<sup>52</sup> (1910), Dienst<sup>26</sup> (1918) Eckelt<sup>28</sup> (1919) and Fahraeus<sup>30</sup> (1921)). A diminution in the depression of the freezing point was also noted in the blood of pregnant women by Zangemeister.

In 1915 Keith et al<sup>45</sup> placed the subject on a more solid scientific basis by establishing the presence of an increased blood volume with a rise in the plasma volume from 50 ccs to 58.4 ccs per kilo of body weight in pregnancy. Dieckmann et al<sup>25</sup> (1934) published the result of their very exhaustive investigations which were carried out on the same women followed throughout pregnancy and showed that the increase in blood volume and plasma volume were not equal but that the former was exceeded by the latter and/

and also that the increase was not a static feature but progressive throughout pregnancy. At the 13th week the blood volume had increased by 16% while the plasma volume had risen 18% over the non-pregnant level. At term the corresponding figures were 23% and 25% respectively. The haemoglobin percentage fell by 15 from the 26th to the 35th week and there was a decrease in haemoglobin per kilo of body weight but a total increase of 13% in pregnancy. The total cell volume was also increased by 20%. The plasma increase is therefore seen to be greater than the increase in cells and haemoglobin and hence the dilution of the blood. By a retrospective method and an arithmetical calculation Strauss and Castle<sup>13</sup> (1932) showed that the red blood cell count in the puerperium corresponds to the figure which one would expect by calculating this figure from the blood volumes before and after delivery. This adds confirmation to the observation of Keith et al that there is a loss of 1100 ccs post-partum which must largely be derived from the increased plasma existing before delivery, since 300 ccs of blood is reckoned as a normal intra-partum loss. Plass and Bogert<sup>78</sup> (1924) had previously shown a fall in the plasma proteins which was maximal at the 6th month and which tended to rise towards full term. Richter et al<sup>82</sup> (1934) in a study of anaemia in pregnancy, showed that this fall in plasma proteins was due/

due in part to a cellular dilution of the blood in the later months. Oberst and Plass<sup>73</sup> (1936) confirmed the results of Dieckmann et al, while Feldman et al<sup>31</sup> (1936) showed an increase in the water content of the blood which decreased in late pregnancy and which was accompanied by a fall in red blood cells, haemoglobin and cell volume per unit of circulating blood. In 1938 Thomson et al<sup>89</sup> discarded the vital red method used by Keith et al and substituted an azo dye method for determining the blood volume. They claimed that this method was more accurate. Again the results were derived from a small number of women each followed throughout pregnancy. An increase in the plasma and blood volumes and in the total red blood cells was shown to start early in pregnancy and to be still greater at a late stage in pregnancy. Evidence was obtained to show a decrease in the blood volume in the 10th lunar month. The increase in cells was not so marked as the increase in plasma and hence the dilution of the blood, although in reality there is a total increase in the solid constituents in circulation.

The nature and the existence of an hydraemia in pregnancy seems to be well established by the work already quoted. In nature the hydraemia appears to be what the name would indicate, namely a watery dilution of the plasma. That this is accompanied by/



by an increase in the total cells and circulating haemoglobin is also established, despite the apparent loss of cells and haemoglobin on ordinary examination. The reasons for this increase in circulating fluid do not seem difficult to find since there is a greatly increased vascular area in the pregnant female which has to be filled. Also it is believed that the blood in the pregnant female acts as a more efficient carrier of nutriment to the placenta than would be the case with normal blood. The more watery nature of the blood seems also to be connected with an increased rate of flow, (Cohen and Thomson<sup>15</sup> (1936)), which would enable greater exchange to take place between mother and foetus. Further the advantages to the individual of a more dilute blood seem obvious when one thinks of the blood loss at delivery. The woman thereby conserves the vital constituents of the blood and is enabled to withstand fairly large blood loss. The main reason, however, is doubtless to meet the needs of the ante-partum period since the changes in blood volume advance with the growing pregnancy.

Is this increase in blood and plasma volume progressive throughout pregnancy? Kuhnell<sup>48</sup> (1926) was early attracted to this aspect of the subject and held definite views that the hydraemia was progressive up to the 34th week and that thereafter there was a diminution. This was shown by a rise in haemoglobin which/

which he said was due to a late diuresis and he believed the change to be so constant as to be of value in determining the duration of pregnancy. The haemoglobin at term, however, never reached the levels obtained before pregnancy started. This work followed 15 individuals throughout their pregnancy. Averaging the results taken from different persons at the same stage of pregnancy and thus obtaining results applicable to every stage, Plass and Bogert<sup>78</sup> (1924) showed a fall in plasma proteins which was maximal at the 6th month and which tended to return to normal towards term. Feldman et al<sup>31</sup> (1936) showed an increased water content of the blood in pregnancy with a tendency to return to normal in the later months. Thomson et al<sup>89</sup> (1938) believed the change towards normal blood volume to occur during the 10th lunar month which is supported by the findings of Labate<sup>51</sup> (1940) who gave the 38th - 40th week as the time at which the hydraemia became less marked, although not disappearing until well on in the puerperium.

Somewhat in contrast to these constant changes we find that Irving<sup>44</sup> (1935), who followed individuals throughout pregnancy, recorded such rapid changes in haemoglobin in the same patient, that the only possible explanation was a rapid change in blood volume, not apparently related to the length or period of gestation. Adair et al<sup>2</sup> (1936) confirm this view which makes it difficult in their opinion to assess the results/

results of treatment by iron during pregnancy.

The weight of evidence is in favour of a steady dilution of the plasma during the greater part of pregnancy with a tendency to return (although not achieved fully in pregnancy) to normality during the last weeks.

It is obviously of some importance to know if possible the amount of this hydraemia since its existence determines the amount of reduction in the haemoglobin percentage occurring in pregnancy. It is not of course accurate to compare two haemoglobins in pregnancy if there is no constant reduction due to hydraemia since each may have started pregnancy with different amounts of haemoglobin and the one may have a greater increase in blood volume than the other. Indeed a perusal of the literature would indicate that the amount of the hydraemia is not constant, as measured by a reduction in the haemoglobin percentage, which is the simplest and only practicable method for use in practice. Dieckmann et al<sup>25</sup> (1934) estimated a fall of 15% haemoglobin as a result of increased plasma volume. At the other extreme Davidson et al<sup>18</sup> (1935) reports a lower level of haemoglobin in pregnant women as compared to non-pregnant, but this lowering is slight and corresponds to the 5% reduction in haemoglobin in Fullerton's<sup>34</sup> two series of women (1937) - the one in pregnancy and the other 9-16 months post-partum by which time hydraemia must have disappeared/



disappeared. Pitts and Packmann<sup>77</sup> (1939) report a reduction of haemoglobin in circulation in pregnancy of 10-15 per cent and also a lower haemoglobin percentage in the sternal marrow as compared to the non-pregnant state. In a review of the subject in 1937 Evans<sup>29</sup> concludes that the evidence is in favour of a plethora in pregnancy but that the amount or extent of this plethora is not fully determined. With this conclusion one would rather agree than with the conclusion of Watson<sup>90</sup> (1938) who found quite a large group of women whose haemoglobin percentage did not differ from normal throughout pregnancy and whom therefore he believes to show no hydraemia. Rather is it likely that this large group (though not so large as the group who showed a reduction within physiological limits) represent those women who have started pregnancy with a haemoglobin level at the upper limit of normality.

The importance of hydraemia in assessing the incidence of anaemia in pregnancy is therefore obvious. A person starting pregnancy with a haemoglobin on the lower limit of normal and showing a marked hydraemia might be thought to be suffering from anaemia of pregnancy. Indeed in some investigations this has been done, but certain features of the anaemia (e.g. spontaneous recovery of blood after delivery, failure to respond to iron, no lowering of the colour index and/

and no reticulocytosis) have persuaded the authors Bland et al<sup>6&7</sup> (1929 and 1930), Galloway<sup>35</sup> (1929), Feldman et al<sup>31</sup> (1936), Watson<sup>90</sup> (1938) and Labate<sup>51</sup> (1940) that the majority have been showing the effects of an hydraemia. Allowing for this hydraemia a lower level of normality for haemoglobin percentage in pregnancy was worked out in an earlier section. This fuller discussion of hydraemia justifies the levels adopted there.

To summarise this discussion on hydraemia we may say that hydraemia is a definite factor in pregnancy, existing for physiological reasons already mentioned. The amount or extent of the hydraemia cannot be definitely stated and is probably not static throughout pregnancy but varies from 5-15%. In arriving at a proper understanding of a haemoglobin percentage in pregnancy, this factor must be given due importance and attention.

#### B. The Puerperal Blood Changes.

That the lowered haemoglobin and increased blood volume of pregnancy eventually reverts to normal is an obvious fact. When and how this reversion takes place is the question requiring to be answered.

It seems obvious that an excessive blood loss at parturition must delay the recovery of a normal haemoglobin level. It is impossible to state what amount is/

is lost at each delivery without laborious investigation, but the normal average amount has been calculated and has been given by various authors to lie between 300 and 500 ccs. of blood.

At first it was thought that it would be possible by a reversal of the method employed by Marriott and Kekwick<sup>64</sup> (1940), in calculating the amounts of blood required for transfusion, to calculate the blood loss at parturition. However, it was soon realised that the alteration in blood volume vitiated this calculation when applied to the immediate post-partum period.

It will be instructive, however, to review some of the literature on this subject of blood loss. The average figure given by Keith et al<sup>45</sup> (1915) was 300 ccs; Thomson et al<sup>89</sup> (1938) in a later study of blood and plasma volume gave 500 ccs as a maximum; Labate<sup>51</sup> (1940) takes 350 ccs as a maximum. As was stated it is impossible for ordinary investigation to be scientifically accurate and therefore only a rough estimate of the loss can be given. The effect of the loss on the subsequent history was well recognised by Fullerton<sup>33</sup> (1936) who stated that the loss was so variable as to render accurate deductions impossible from the results of haemoglobin estimations in the puerperium. However he was able to show the importance of moderate loss and severe loss in parturition in 15 women, otherwise comparable. Seven who had a severe/



severe loss showed a rise of 5% in nine days and a rise of only 6% after a few weeks in the haemoglobin levels found at the end of pregnancy. In 8 others with a normal loss the corresponding figures were

5% and 21% respectively. It is seen therefore that average results in a series of cases can only assume an accuracy if obvious cases of severe loss at parturition are excluded.

The blood and plasma volume studies and the effect on the various constituents of the blood help us to understand the mechanism of the reversion to normal after the alteration of the blood in pregnancy.

Keith et al<sup>45</sup> (1915) reported a loss of 1100 ccs of fluid during the first ten days of the puerperium as a result of lowered blood volume. There was no alteration in blood volume for the first 36-48 hours. There is a return of the plasma proteins and the water content of the plasma to normal at the end of one week after delivery according to Plass and Bogert<sup>78</sup> (1924) and Oberst and Plass<sup>73</sup> (1936). These changes begin to take place before actual parturition. The haemoglobin content does not return to normal so quickly. Oberst and Plass<sup>73</sup> (1936) showed that although the haemoglobin per 100 ccs of blood was lower than normal at term due to hydraemia yet the haemoglobin content of each red cell was 7% above normal. After delivery this increase in haemoglobin begins to return to normal and at/

at the end of the second week after delivery the haemoglobin per 100 ccs is the same as at delivery. This agrees with the findings of Dieckmann et al<sup>25</sup> (1934) who showed that the haemoglobin per 100 ccs is 17% below normal after 2 weeks from delivery and still 14% below normal at the end of eight weeks. The red blood cells have returned to normal levels by the third post-partum week and the blood volume has also dropped to normal by the eighth week. The return of blood and plasma volumes to normal was shown by Thomson et al<sup>89</sup> (1938) to take place in two weeks after delivery by the loss of 1,226 ccs of fluid. It is apparent then that the blood volume rapidly re-adjusts itself to the lessened requirements of the non-pregnant state. The red blood cells are able to return to normal levels speedily but experimental evidence points to a slower return of the haemoglobin level to normal figures.

The speed of recovery of red blood cells and the relative slowness of recovery of haemoglobin is further exemplified by certain clinical studies on red blood cell counts and haemoglobin estimations. Although it is doubtful if the 48 patients examined by Bland et al<sup>7</sup> (1930) were all truly anaemic, yet even in this group a gain of 200,000 r.b.cs. per cmm. is shown within 10 days of delivery in 71% of these cases. The red blood cells had returned to normal in 10 days in 11 patients having a normal blood loss at/

at delivery (Labate<sup>51</sup> (1940)). McGeorge<sup>61</sup> (1935) followed 94 women throughout pregnancy and the puerperium and reported that the haemoglobin was still 6% below normal up to the fourth week post-partum and 8% below normal up to the fourteenth day. At the 10th day Labate<sup>51</sup> (1940) found his normal patients to be 9% below normal levels for the non-pregnant. The results of others though not so specifically stated agree regarding the slow return to normal haemoglobin levels. Bland<sup>6&7</sup> (1929 and 1930) gives a period of 6 months for this return to normal. Watson<sup>90</sup> (1938) found none of his patients anaemic between 6 and 9 months after delivery. Fullerton<sup>33</sup> (1936) found a steady rise in haemoglobin up to 6-11 months after delivery. In 34 cases studied the average haemoglobins were 75.4% a few days off full-term, 69.9% within 48 hrs. of delivery and 74.7% on the 9th day post-partum. None showed a fall between 48 hours and 9 days post-partum. After 5 months Galloway<sup>35</sup> (1929) showed his patients to have an average haemoglobin of 83% (Sahli), but this rise was not progressive. There was a drop during the first 48 hours after delivery, followed by a rise during the fortnight in hospital, but the effects of this rise were lost at the end of eight weeks, after which time there was a steady improvement. This fall after leaving hospital was also noted by Davis and Walker<sup>23</sup> (1934) who attributed it to the altered/



altered environment and increased duties of most of the women. Richter et al<sup>82</sup> (1934) also noted a maximal fall in haemoglobin level post-partum at the end of the 6th week with recovery thereafter.

The normal train of events after delivery in regard to blood and plasma volume, red blood cells and haemoglobin seem to be well established. Co-incident with this return of the blood to normal Strauss and Castle<sup>12</sup> (1932) showed a return to normal of the gastric acidity. No definite co-relation between these two facts can be drawn and we would seem to have an indication here that the gastric acidity has no aetiological role to play in the regulation of the haemoglobin level. This will be fully discussed later when considering the Anaemia of Pregnancy.

This survey of the literature would therefore lead us to the conclusion that there is a definite return of the haemoglobin towards normal levels during the puerperium. The early changes in red blood cells and haemoglobin are probably due to reduction in the hydraemia and not to an haematopoiesis. A definite steady rise in haemoglobin may not begin to take place until after 6 weeks from the time of delivery, since most authors show fluctuations, particularly in the haemoglobin level in the first days and weeks of the post-natal period. A return to normal haemoglobin levels may be delayed some months, six months appearing/

appearing to be a reasonable estimate from the literature. The red blood cells return to normal figures more quickly than the haemoglobin, therefore a hypochromic anaemia must exist at some stage during the early weeks of the post-partum period. This raises an interesting point for discussion but will necessarily be considered under the effects of iron therapy.

#### Own Results of the Blood Changes in the Puerperium.

From amongst the 104 cases studied, 21 were eventually placed in a control group for pregnancy and the puerperium. These cases fulfilled the requirements already laid down in regard to the anaemia level of haemoglobin. None fell below this standard at any time in pregnancy or the puerperium. No case had received iron therapy at any stage. There was no excessive blood loss at parturition. These 21 have already been included as controls amongst the 40 normal controls in pregnancy. The remainder of the 40 received iron in the puerperium and therefore cannot be considered here.

All the cases except 4 were followed throughout the greater part of pregnancy and during the first 6 weeks or so of the post-partum period. The 4 exceptions were cases referred to the Maternity Hospital by other doctors. These were seen either just before or at the commencement of labour and they were followed/

followed until their discharge from hospital usually between the 12th and 14th days of the puerperium. None of these cases had received any iron therapy from the doctor in charge of the ante-natal period. The presence or absence of ante-natal anaemia had to be gauged from only one or two readings of the haemoglobin before or at term. As will be mentioned in this section later, it is possible that some of these cases may have been mildly anaemic earlier in pregnancy, but the fact that the haemoglobin was not known to fall below the standard included them in this normal control group.

Graph II shows the curve of the calculated averages of haemoglobin for the different periods of pregnancy and the puerperium. The calculation of the averages in pregnancy is based upon the same time intervals as in Graph I. After delivery the averages were calculated daily for the first nine days and thereafter at the times shown on Table V. This table gives the details from which Graph II was constructed.

See TABLE V.

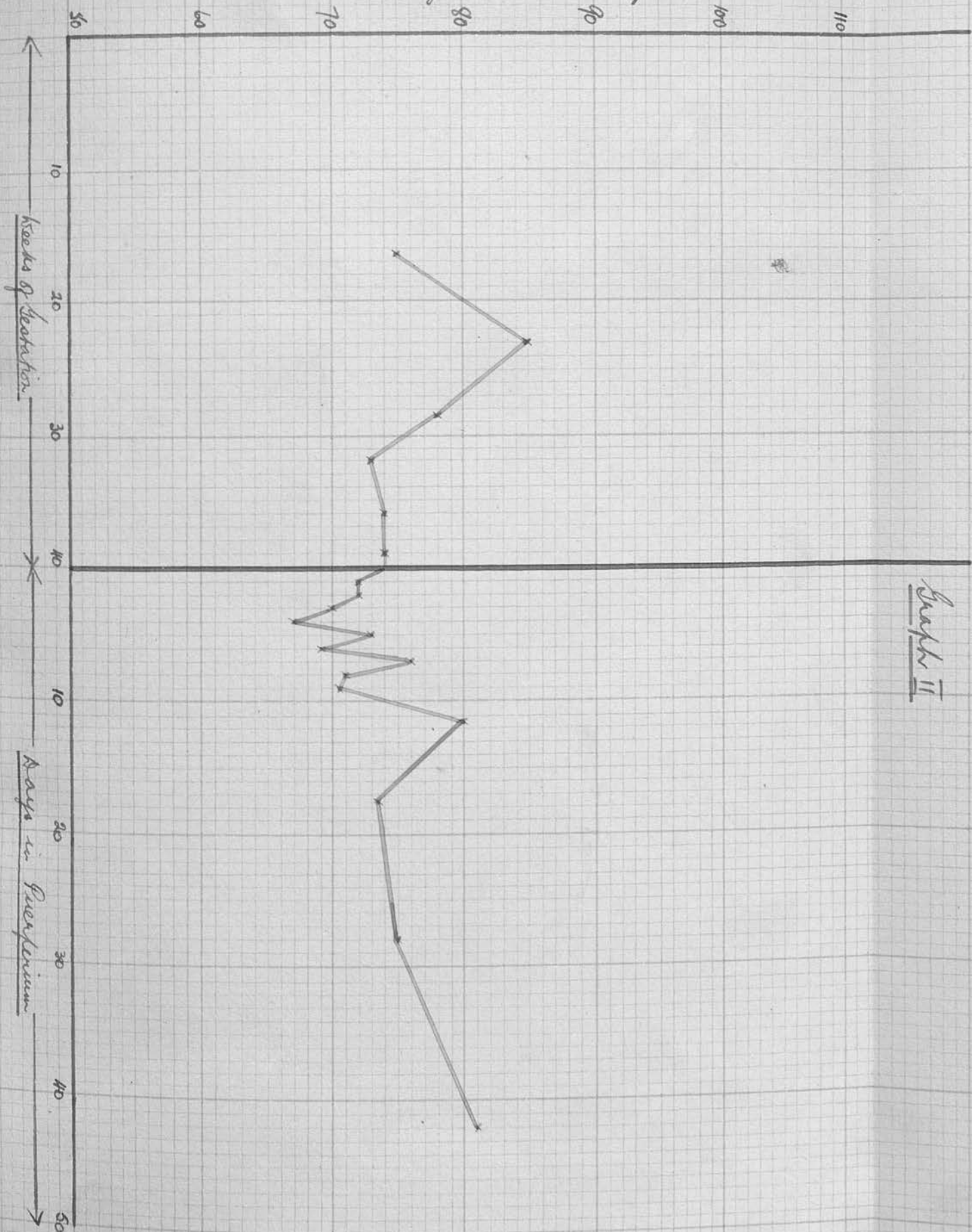
The graph shows the fall in haemoglobin in the third trimester of pregnancy which was noted before. The two earlier readings are probably inaccurate on account of the small numbers of readings from which they are derived. This group does not show the rise in haemoglobin in the last two weeks of pregnancy which/



418.

Graph II

Haemoglobin Percentage.



Weeks of Gestation.	13 - 19	20 - 26	27 - 30	31 - 34	35 - 38	39 - 40
No. of Results	2	4	5	5	15	28
Range %	65 - 85	79 - 90	76 - 80	68 - 81	65 - 87	60 - 90
Av. Hgb. %	75	85	78	73	74	74

Days of Puerperium.	1	2	3	4	5	6	7	8	9	10-14	15-21	22-35	36-60
No. of Results	22	15	12	6	9	6	7	6	2	26	6	6	14
Range %	61-88	65-85	57-90	60-80	65-90	63-80	67-92	65-83	66-75	70-103	66-80	65-87	70-93
Av. Hgb. %	72	72	70	67	73	69	76	71	70+5	80	73-5	75	81

Number of Cases from which results were obtained = 21.

TABLE V.

which was seen in the larger control group (Graph I), but here, as was mentioned earlier in this section, there are included those cases seen only at term who had rather low readings of haemoglobin for such a late period of pregnancy (viz 63, 66, 69 and 71) and who might well have earlier shown a mild anaemia. Excluding these four cases the average for the last two weeks of pregnancy becomes 75% instead of 74%.

The puerperium is the period of particular interest at present.

At first it was possible to take frequent readings of the haemoglobin during the first 24 hours in the endeavour to follow closely the rise and fall of the haemoglobin following the blood loss of parturition. However, it was soon seen that little was to be learned from readings at 3, 6, 12 hours etc., and thereafter daily readings were taken as previously described.

It was customary to find variations in the haemoglobin from day to day, especially during the first four days of the puerperium. The haemoglobin percentage usually reached its lowest on the fourth day and this is shown by the average on the graph. From then until the 9th day - this being the usual day on which the patients were allowed up for the first time - there was a general tendency to a rise in haemoglobin. The rise was maximal before discharge which usually took place between 10 and 14 days after delivery/



delivery. The cases investigated between this time and the completion of six weeks showed a fall below the level attained at discharge. This was noted by Galloway<sup>35</sup> (1929) and Davis and Walker<sup>23</sup> (1934) and the increased duties and altered environment were believed by these authors to be contributory factors to this fall in haemoglobin.

At the end of six weeks the level attained by the average is 81%, which was also found to be about the average for the other normal groups to be considered later. This still falls below the average normal for the non-pregnant state, but at this time the haemoglobin appears to be taking an upward course. It was not possible to follow these women until 6, 9 or 12 months after delivery, but probably the rise was not maximal at the end of six weeks. The results do not agree with those who found a maximal fall at the end of six weeks (Richter et al<sup>82</sup> (1934)) and a steady rise afterwards (Galloway<sup>35</sup> (1929)).

To summarise these results we may say, that after delivery there is a fall in the haemoglobin percentage for the first four days. This fall is probably due to blood loss, but the drop in haemoglobin percentage cannot be used to calculate the blood loss at parturition, since there are daily fluctuations in individual cases. After the fourth day there is a rise up to the end of the lying-in period of about 14 days.

During/

During this period the woman's environment is optimal. With the return to duty and an altered environment, there is a fall in haemoglobin between the end of the second and the sixth week. By the end of the sixth week after delivery there is a return of the haemoglobin towards normal, but completely normal figures may not be reached for some months afterwards.

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## ANAEMIA IN PREGNANCY.

Our discussions and investigations thus far have enabled us to understand the normal course of events regarding the altered blood picture of pregnancy especially in respect of the haemoglobin. We have also been able to establish ranges and lower limits of normality for the non-pregnant as well as the pregnant state. So much may be regarded in some ways as an introduction to the study of anaemia as found in pregnancy. It is with the anaemia of pregnancy that we are mostly concerned, since this is the condition which clinically and practically concerns both doctor and patient. We may anticipate a later discussion on the anaemia of pregnancy, by stating, that all the cases met with in this series presented the hypochromic type of anaemia.

### The Incidence of Anaemia in Pregnancy.

Once more a perusal of the literature shows the diversity of methods which have been used by various authors to establish the haemoglobin percentage of their cases. Realising this Boycott<sup>8</sup> (1936) converted the readings of the other authors studied into Haldane Scale equivalents. In the present consideration of the known facts it has been found to be more accurate to refer to the haemoglobin levels as Gms. of Haemoglobin per 100 ccs of whole blood.

Allowing for this error which occurs in comparing  
haemoglobin/



haemoglobin levels, before conversion to a comparable scale, yet there are great discrepancies for the figures even after this conversion. This is due in part to the fact that different authors have adopted different standards of anaemia. An attempt has therefore been made to calculate, where possible, the percentage of anaemic patients in each series, adopting a constant figure of 10.0 Gms. per 100 ccs as the level below which anaemia exists. The reason for adopting this level has already been discussed. Unfortunately the bulk of the figures given in the literature do not enable this to be done accurately and a glance at column six of Table VI will show that the percentage of anaemic patients can only be expressed as  $>$  or  $<$  a certain number.

Other factors arise making strict comparison impossible. The chief of these is the hydraemia of pregnancy. Many authors have included these cases in their series of anaemic patients - while realising that they are not truly anaemic as judged by the colour index (cf. Fullerton<sup>33</sup> (1936)) and their return to normal after delivery without treatment. This is particularly so of the earlier reports in the series where the percentage of anaemic patients is high compared to the bulk of the later reports. Other authors have attempted to make allowance for these cases not truly anaemic or in other words showing the effects of hydraemia and their results have therefore shown a/

a lower percentage of anaemic patients.

Another source of difficulty in making comparisons and in estimating the percentage of anaemic patients has been the fact that some authors have adopted the anaemic standards of the non-pregnant and applied them to the pregnant woman. Even amongst this group the standards of anaemia vary and again the reduction allowed for hydraemia varies from 5% (Fullerton<sup>33</sup> (1936)) to 10% (Ramsay et al<sup>80</sup> (1938)).

Confusion also exists as to what is meant by anaemia in pregnancy. Usually the figures quoted include patients showing a reduction in haemoglobin below a certain level, making allowance for hydraemia in some instances. Below this level there are those cases showing a reduction in haemoglobin as a direct outcome of the pregnancy (cf. Boycott<sup>8</sup> (1936)) a true pregnancy anaemia. There are others whose anaemia has an obvious cause (i.e. a true secondary anaemia) e.g. haemorrhage, nephritis, pyelitis etc. (cf. Boycott). Also there are those with a reduced haemoglobin who are believed to be manifesting signs of a pre-existing hypochromic anaemia which may have been made more obvious by the hydraemia of pregnancy. The chief advocate of this theory is Fullerton<sup>33</sup> (1936).

Leaving aside any further discussion of the nature of the anaemia of pregnancy at this stage it may be assumed that all the figures quoted included all cases with reduced haemoglobin and the explanation given/

given by the author of the cause does not usually enable him to divide his cases into groups. At any rate for the purpose of assessing the incidence of anaemia, the definition of anaemia is a reduction of haemoglobin below 10 Gms. per 100 ccs, a level below which hydraemia cannot be considered to operate alone.

Turning now to a consideration of the results tabulated (Table VI) an attempt will be made to assess the incidence of anaemia in pregnancy. Lyon<sup>57</sup> (1929), Galloway<sup>35</sup> (1929) each using a Sahli haemoglobinometer, but each failing to state the calibration of their instrument have given different levels for the occurrence of anaemia. The level of anaemia in Gms. per 100 ccs. has been calculated using 100% Sahli equal to 15.8 Gms. per 100 ccs. This differs from the figure of 17.3 Gms. equal to 100% Sahli which was used by Boycott for his conversion of the figures of these two authors. There seems to be no justification for the use of such a high equivalent by Boycott. Taking the lower figure used here the percentage of anaemic cases is high. Reducing the level of anaemia to 10 Gms. per 100 ccs of blood, this might reduce Lyon's incidence considerably, but Galloway's would probably still be very high. Bland et al<sup>6</sup> (1929) stated that 92% of their anaemic cases responded after delivery without treatment and therefore only 8% were truly anaemic. In a second series by the same authors in 1930<sup>7</sup> 73.5% were below 10.35 Gms. per 100 ccs. but

20/



Author.	No of cases.	Method of Hgb. Estimation.	Author's "Anaemia level" of Haemoglobin.	% age Anaemic. (Author's Figures).	% age Anaemic (i.e. below 10.0 Gms Hgb %.)	Remarks.
Lyon. 1929.	177.	* Sahli.	70% = 11.06 Gms.	32.2%	< 32.2%	* No standard given. Standard taken 100% = 15.8 Gm% cf. Boycott.
Shalloway. 1929.	222	* Sahli.	65% = 10.35 Gms.	65.0%	< 65.0%	* ditto ditto.
Bland et al. 1929.	.	-	75% = 10.35	* 8.0%	-	* 92% of Anaemic cases in Pregnancy respond after delivery. No fall in C.I.
Bland et al. 1930.	300	Dale.	75% = 10.35 Gms.	* 75.3%	-	* cf. same author. States that 20 out of 23 below 75% recover. ∴ Hydraemia.
Moore. 1930.	300	* Haldane.	80% = 11.04 Gms.	* 50.0%	* > 16.3%	* Not definitely stated. * Require treatment. * Standard = 9.67 Gm.
Strauss & Castle. 1933.	.	-	Not Stated.	* Probably high.	-	* No Fall in C.I. ∴ Probably many Hydraemic.
Davies & Shelley. 1934.	51	Haldane.	* 75% = 10.35 Gms.	12%	< 12%	* From Davies 59. 1935.
Davis & Walker. 1934.	69	-	70%	64%	-	Colour index always about unity ∴ suggests hydraemia.
Richer et al. 1934.	99	Sahli.	* 70% = 10.36 Gms.	78%	* > 78%	* This level adopted from Author's figures. * allowing for hydraemia author assesses anaemia at 11%.
McGeorge. 1935.	100	Helligen.	75% = 10.35 Gms.	16%	< 16%	
Stearns & Gottlieb. 1936.	75	-	75% = 10.50 Gms.	38.7%	< 38.7%	
Bethell. 1936.	66	Sahli.	70% = 11.06 Gms.	70%	< 70%	
Adair et al. 1936.	8005	-	10.16 Gms.	* 11.6%	< 11.6%	* If haemoglobin standard of anaemic for non-pregnant taken, then % anaemic = 63.2
Boycott. 1936.	222	Haldane.	* 80% = 11.04 Gms.	22%	* > 11% - 16.8%	* Author qualifies this level - See Text * See Text.
Reid & Mackintosh. 1937.	1108	Haldane.	70% = 9.67 Gms.	10.2%	> 10.2%	
Davidson & Fullerton. 1938.	819	Haldane.	80% = 11.04 Gms.	49.5%	< 49.5%	
Ramsay et al. 1938.	96	Dale.	60% = 9.6 Gms.	7.37%	> 7.37%	Author allows 10% drop in Hgb. for hydraemia.
Watson. 1938.	500	* Sahli.	55% = 7.7 Gms.	5%	> 5%	* 100% = 14 Gms%.
Lababe. 1939.	881	O <sub>2</sub> Capacity.	80% = 11.6 Gms.	48%	< 48%	325 anaemic cases treated did not rise above 11.17 Gms ∴ anaemia level too high.

Table VI.

serve for comparison as they cannot be calculated to the level already quoted. Adair et al<sup>2</sup> (1936) in a very large series adopted a level for anaemia in pregnancy of 10.16 Gms. which is close to the level selected in this study. From this series reported by Adair et al there were only 11.6% anaemic. Appreciating the fallacy of adopting non-pregnant standards for pregnant women, these authors point out that if non-pregnant standards were adopted their incidence of anaemia would rise to 63.2%. The results of Boycott<sup>8</sup> (1936) also illustrate this point. Adopting a level of 11.04 Gms. at the outset, 22% (50 cases) were shown to fall below this level. However, the closer study of some of these anaemic cases showed that half of these with no obvious cause for the anaemia, really manifested the hydraemia of pregnancy. The other half (13 cases) he believed manifested the true anaemia of pregnancy, while others showed a true secondary anaemia. 10 cases of the 22% (50 cases) were not fully investigated and therefore excluded. Omitting the 13 cases known to show hydraemia, we obtain a percentage for the anaemic cases below 11.04 Gms, of 11% or 16.8%, depending upon whether we exclude or include the 10 cases not fully investigated. These figures would be lowered on the basis of 10 Gms. adopted here. Reid and MacIntosh<sup>81</sup> (1937) took the level of anaemia to be 9.67 Gms. and showed an incidence of 10.2%. The figure of 49.5% given by Davidson and/

and Fullerton<sup>19</sup> (1938) for anaemia in pregnancy would be lower on the basis of 10 Gms. for the level of anaemia, but allowing for this, the figure would probably still be high. This fact seems to be generally appreciated by most authors and the reason for the high figure is usually believed to be the fact that the investigation included only very poor women in Aberdeen, who were shown to have a high incidence of anaemia even in the non-pregnant state. (Davidson et al<sup>18</sup> (1935)). This earlier investigation of 819 pregnant women showed a parallel but lower curve of haemoglobin as compared to the non-pregnant. The latter showed 17% of anaemia, therefore the pregnant must have shown a similar percentage after making allowance for the hydraemia of pregnancy. The figures given by Ramsay et al<sup>80</sup> (1938) and Watson<sup>90</sup> (1938) would require to be raised to the level adopted here in order to be strictly comparable. Watson's figure of 7.7 Gms. for the level of anaemia would appear to be unduly low, considering all other workers. Labate<sup>49</sup> (1939) adopted a high level of haemoglobin as representing the lower limit of normal and therefore the incidence of anaemia was high. However, he admits that treatment of 325 cases failed to raise the haemoglobin above 11.17 Gms. This means that the level adopted for anaemia is too high and also that many probably manifested hydraemia.

Superficially the results of authors from different/





different countries vary but when compared on a similar basis the variation is not great and certainly no greater than that recorded by different workers in the same country. Social status would appear to be a factor as the results of the workers in Aberdeen are higher as regards incidence of anaemia than those of others who never worked solely amongst the very poor. This will be more fully discussed later along with such factors as age and parity. For the present however, the effect of these two latter does not appear to be great.

It is difficult if not impossible to give any average figure from the above facts, which would be at all accurate. However, in the light of the above discussion it seems fair to estimate the percentage of anaemia in pregnancy as somewhere in the region of 10%, probably slightly more. The figure given by Davidson et al<sup>18</sup> (1935) and applied to the results of Davidson and Fullerton<sup>19</sup> (1938) has been reduced to 17% as explained above and this would appear to be the highest recorded incidence amongst those where due allowance has been made for hydraemia. Quoting Boycott<sup>8</sup> (1936) we may say that anaemia in pregnancy, in countries where the hypochromic type is most usually seen, is not a factor of such great magnitude as at first seems likely.

Incidence/

### Incidence of Anaemia in Own Results.

The standards laid down have already been fully discussed. The analysis of the 104 cases has been undertaken with a view to considering those complications of pregnancy and the puerperium most likely to affect the blood condition. Therefore only certain abnormalities and complications appear in the results.

See TABLE VII.

From the above table it will be noted that eight cases showed only a hypochromic anaemia during pregnancy and no other complication of pregnancy or the puerperium. No case of anaemia with a colour index over unity was seen. Three other cases must be included with these eight as having manifested a hypochromic anaemia in pregnancy; these three had an excessive blood loss at labour and helped to make up the total of 12 who were grouped together as having had an excessive blood loss at parturition. These three showing anaemia before labour and an excessive blood loss at labour, were all included in the 9 who showed a secondary anaemia during the puerperium. The total number showing a hypochromic anaemia and no other abnormality during pregnancy was therefore 11 or 10.57%.

One case has been classified as a secondary hypochromic anaemia of pregnancy, since there was the complicating/

	"Anaemia of Pregnancy"		P.P. Sepsis		Toxaemia		Secondary Anaemia	
	A.P.	A.P. Sepsis (Pyelitis)	A.P. Sepsis (Pyelitis)	Pyelitis Breasts Pelvic	Hyperem. Album. Haem.	A.P. P.P.	A.P. P.P.	A.P. P.P.
"Anaemia of pregnancy"	8							
A.P. Sepsis (Pyelitis)		5	1*			1*	1*	1*
Pyelitis			2					
Breasts			5			1*	2*	2*
Pelvic				3		1*	2*	2*
Hyperemesis					1	1	1	1
Albuminuria			1			5	1*	1*
P.P. Haemorrhage	3**					12	9**	9**
Totals	11	5	3	3	1	5	16	16
Percentages	10.57	4.80	2.88	5.76	2.88	0.96	4.80	15.37 0.96 15.37

\* means the same patient is concerned in each horizontal group.

TABLE VII.



complicating factor of pyelitis of pregnancy in this case. If we include this case, with the 11 others showing hypochromic anaemia, we have a total of 12 anaemic cases or 11.5%.

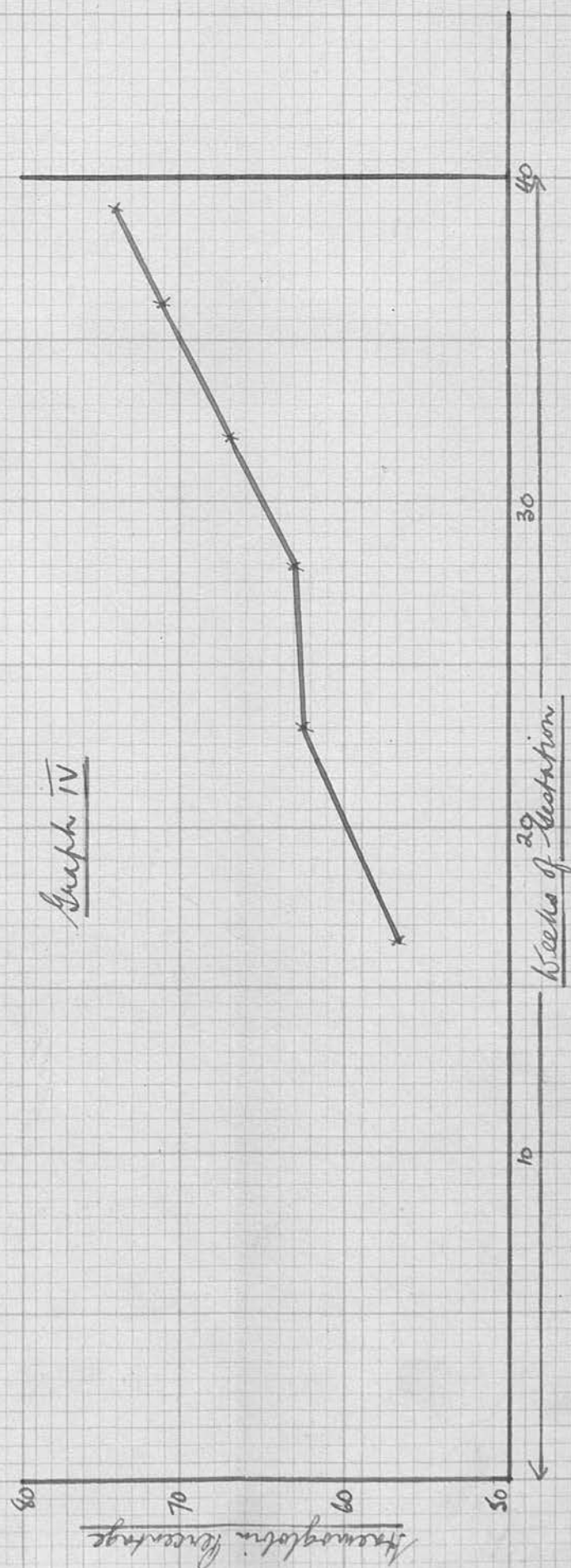
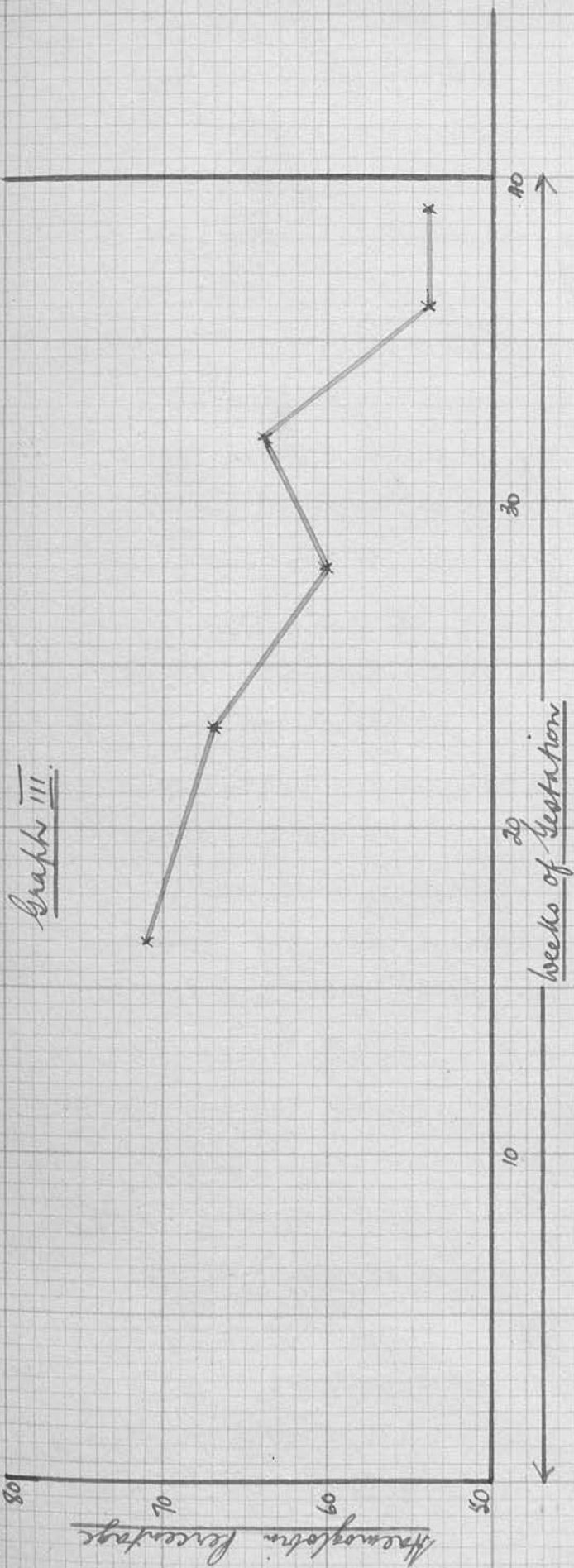
A closer analysis of these anaemic cases shows that none had a hyperchromic anaemic. When the haemoglobin fell below 60% (Sahli) and a red blood cell count was done, it was always found that the red cells were not reduced to the same extent as the haemoglobin. In no case did the red blood cells fall below  $3.5 \times 10^6$  per cmm. and then only in the most markedly anaemic. The colour index was below 0.8, calculating this after the Sahli percentage had been converted to the Haldane scale. Clinically, these cases varied in severity. Most complained of easy fatiguability and only the most severely anaemic complained of shortness of breath on exertion and swelling of the ankles. Most were obviously anaemic as judged by the pallor of the conjunctival mucous membrane. This pallor was not a feature of the normal cases.

The inclusion of one case in this group seems doubtful. She was first seen at the 33rd week of pregnancy and had a haemoglobin of 60% and no symptoms of anaemia. She was left untreated for three weeks and at that time the haemoglobin had fallen to 54% but still no symptoms could be elicited and no signs of ill effects from the anaemia could be made out.

Treatment/

Treatment was therefore still withheld and before term the haemoglobin had risen above 60% and still continued to rise during the first six weeks after delivery, although the rise was not striking. She has been included as amongst the anaemic since the haemoglobin had fallen below 60% (Sahli). If it had been possible to have earlier readings before the 33rd week it would have been easier to judge whether or not a true anaemia existed. This case has not been included in the Graph III.

The other seven uncomplicated cases of anaemia in pregnancy were divided into two groups. The first consisting of three cases treated with iron from the time of the anaemia becoming manifest. The second of four cases who were classed as untreated. One of this latter group was seen only shortly before labour started, having been referred to the hospital for her confinement. Her haemoglobin at term was 50%. Two others were only seen for the first time a few weeks off term and probably only reported then on account of excessive tiredness and swelling of the ankles with dyspnoea on exertion. They were multiparae of the type who never trouble a doctor during pregnancy unless compelled to for some reason such as the above. Although given iron for their anaemia the period of treatment fell short of the eight weeks which was adopted as a minimum for effective treatment. In neither/





neither was an apparent response to treatment seen and one proved very erratic in her taking of the iron. Both, therefore, were classed with the untreated. The fourth in this group showed only a mild anaemia and was left untreated for experimental purposes. So far as can be judged, the anaemia in these cases developed late and certainly seemed to become worse in the latter weeks of pregnancy. There was one untreated case who was seen late in pregnancy with a mild anaemia and who showed an excessive blood loss at delivery. This patient has been included with the other four untreated cases in order to compile the Graph III which shows the deterioration in the blood condition as pregnancy advances. The numbers involved are small but the results interesting especially as a comparison to those in Graph IV.

Of the three anaemic cases treated with iron in pregnancy, two were seen to develop the anaemia before the 20th week of gestation. The third case was seen for the first time at the 29th week when the haemoglobin was 50% (Sahli). Two cases treated with iron in pregnancy showed excessive blood loss at delivery but are considered here with the other three and help to compile Graph IV. These five cases showed a good response to iron and the composite Graph IV for this group is in striking contrast to Graph III for the untreated group. The fuller consideration of the response to iron will be given in the next section on/

on Iron Therapy.

This discussion of the incidence of anaemia in this series of cases enables us to say that the cases all showed a hypochromic anaemia which tended to become worse, as pregnancy advanced, if untreated. In the treated group the anaemia appeared early and may also have been present early in the untreated group, but the facts do not permit any definite opinion. The incidence of anaemia in pregnancy was 10.57% or 11.50% if one case with a secondary anaemia due to pyelitis is included.

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## IRON THERAPY AND ITS EFFECT ON THE BLOOD PICTURE.

Thus far the normal behaviour of the blood in pregnancy and the puerperium and the incidence of hypochromic anaemia have been considered. The point of greatest interest is to know whether these conditions can be affected by treatment, to the advantage of the patient. Knowing the occurrence of an anaemia in pregnancy many investigators have been concerned with the administration of iron to women in pregnancy. Our purpose now is to study the results of iron therapy in pregnancy and the puerperium and to find out just what advantage, if any, results to the patient either during the period of pregnancy or in the period after parturition. This study will be illustrated from the literature and from one's own observations which have been particularly directed to this end.

### A. Pregnancy.

In the consideration of the incidence of anaemia in pregnancy, it was noted that many, if not most authors considered this to be a major problem and therefore it has been a frequent experiment to administer iron routine in pregnancy in order to note its result. However, we have shown that, while figures probably vary from place to place, the incidence of true anaemia, as distinct from the physiological hydraemia, is probably nowhere very high. A consideration/



consideration of the results of iron therapy in pregnancy immediately leads one up against this distinction which is not always clearly stated or apparently appreciated by certain authors. This subject will therefore be discussed under the headings of hydraemia and anaemia.

1. Hydraemia. Patients showing a reduction of red blood cells and haemoglobin consequent upon an increase of plasma volume would not at first sight be expected to show any iron lack, and therefore supplying extra iron by mouth would not be expected to make any alteration in the haemoglobin level which has been reduced by dilution and not by any iron shortage. The results of Mackay<sup>62</sup> (1931) support this theory, for in 23 cases given iron in pregnancy there was no advantage compared to an untreated group, as regards the haemoglobin level at 20 and 19 days respectively before delivery. These cases all started with a haemoglobin level in 70% but the large groups - which included a few anaemic patients - of 39 controls and 44 treated patients showed a similar result. The value of iron in the group which McGeorge<sup>61</sup> (1935) terms slight or moderate anaemia is not proven by his results which are as good for those without iron as those with iron. Adair et al<sup>2</sup> (1936) noted marked and rapid fluctuations in haemoglobin level in pregnancy and doubted the value of haemoglobin estimations as/

as an index to the efficacy of iron therapy. They conclude that the physiological lowering of the haemoglobin cannot be affected by iron therapy. This also is the conclusion of Labate<sup>51</sup> (1940) in the cases showing hydraemia. 55% of 456 cases having a normal haemoglobin at delivery had received no treatment. These 456 represented 52% of the whole series (Labate<sup>49</sup> (1939)) the remaining 48% had some degree of anaemia according to the author's standards.

While these authors agree that there is no result to be obtained from administering iron to patients with a physiological lowering of red blood cells and haemoglobin, yet it must be admitted that others have found the opposite. Some have been in favour of using iron routinely in pregnancy (Evans<sup>29</sup> (1937)) because of the increase obtained in the haemoglobin level towards the end of pregnancy. Most of the 65% of 382 cases investigated by Galloway<sup>35</sup> (1929) showed a favourable response to iron. These 250 cases were considered to be anaemic, but doubtless most manifested only the physiological hydraemia and therefore the figures favour the possibility of some response to iron even in cases of hydraemia. Patients considered by Mussey et al<sup>70</sup> (1932) to show anaemia were divided into a control and a treated group. The latter showed a rise in haemoglobin in each trimester, as against a fall in the untreated group. They noted however, /

however, that iron could only raise the haemoglobin level to 66% (Dare). The influence of hydraemia is therefore at work, but in each group there were doubtless cases of true anaemia, the effect of which would be to show an average increase in the treated group. We cannot however rule out the possibility of some response to iron even in the condition of hydraemia. Likewise the six patients out of 51 normal pregnancies whom Davies and Shelley<sup>22</sup> (1934) considered to be anaemic only responded up to a certain level of haemoglobin as a result of iron therapy. The same remarks therefore apply as to the cases of Mussey et al. Comparable to these results are those of Davis and Walker<sup>23</sup> (1934) who showed that treatment with iron prevents a fall in haemoglobin in the second and third trimesters; Richter et al<sup>82</sup> (1934) whose 38 treated cases showed an improvement over 61 control cases; Irving<sup>44</sup> (1935) who noted the effects of hydraemia but yet showed an improvement in the haemoglobin before delivery in his treated group. All of these must undoubtedly have contained anaemic cases in both control and treated groups, since no attempt was made to sift the cases, therefore, the response to iron is in some measure explained. The striking results of Moore and Pillman-Williams<sup>69</sup> (1936) who showed an average rise of 17% haemoglobin in pregnancy in their treated group and a fall of 8% in the untreated, seems to defy any reasonable explanation. Also the results of Gottlieb/



Gottlieb and Strea<sup>37</sup> (1939) may be questioned since the authors claim that in the 250 treated cases all return to normal in 4 to 6 weeks. No other author has attempted to make such a generalisation. The results of Smallwood<sup>84</sup> (1936) showing a slight advantage for the 59 treated cases over the 106 untreated seems typical of what one might expect. In part this is due to the inclusion of some anaemic patients in each group, but theoretically a slight response might be expected in certain hydraemic cases. Widdowson<sup>93</sup> (1939) giving iron to women in pregnancy reported a rise in their average haemoglobin as compared to a normal control group. This advantage only lasted so long as the administration of iron was continued and as soon as the iron was stopped the haemoglobin of the treated cases began to drop as in the untreated. This advantage was admitted by the author to have no statistical significance, but she considers it suggestive of the benefit of iron in normal cases. The assumption of Fullerton<sup>33</sup> (1936) is that the increased blood volume acts as a stimulus to red blood cell formation in certain cases and if the iron reserves are low the new cells would show a lower haemoglobin content without necessarily falling into the truly anaemic group, as there would still be an absolute increase of haemoglobin in circulation. If such a condition can be assumed then it would explain/

explain the limited response of certain cases showing hydraemia. Where a striking response to iron is obtained it must be assumed that the cases manifest anaemia and not a pure hydraemia. Assuming with Widdowson<sup>93</sup> (1939) that her administration of iron to normal pregnant women gives a rise in haemoglobin, it is possible that the explanation given by this author is a more reasonable explanation than that given by Fullerton and just mentioned. Widdowson believes that the stimulus to haemoglobin formation is the level of the plasma iron and this is temporarily raised during iron administration since the absorption of iron depends upon the relative concentrations in the bowel lumen and in the plasma and the former is abnormally raised by giving massive doses of iron. The same results and conclusions are to be drawn from the work of Widdowson and McCance<sup>97</sup> (1936) and Sankaran and Rajagopal<sup>98</sup> (1938) working with men and non-pregnant women. However, from the more recent work of Fowler and Barer<sup>101</sup> (1941), who administered iron for more than 12 weeks and found at this time a peak rise in haemoglobin and a subsequent steady fall to normal levels despite continued iron therapy, it appears that the rise following iron therapy in normal individuals is a supernormal rise and not a rise indicative of any iron deficiency.

Our study of the literature therefore leads us to conclude that iron given to normal non-pregnant women/

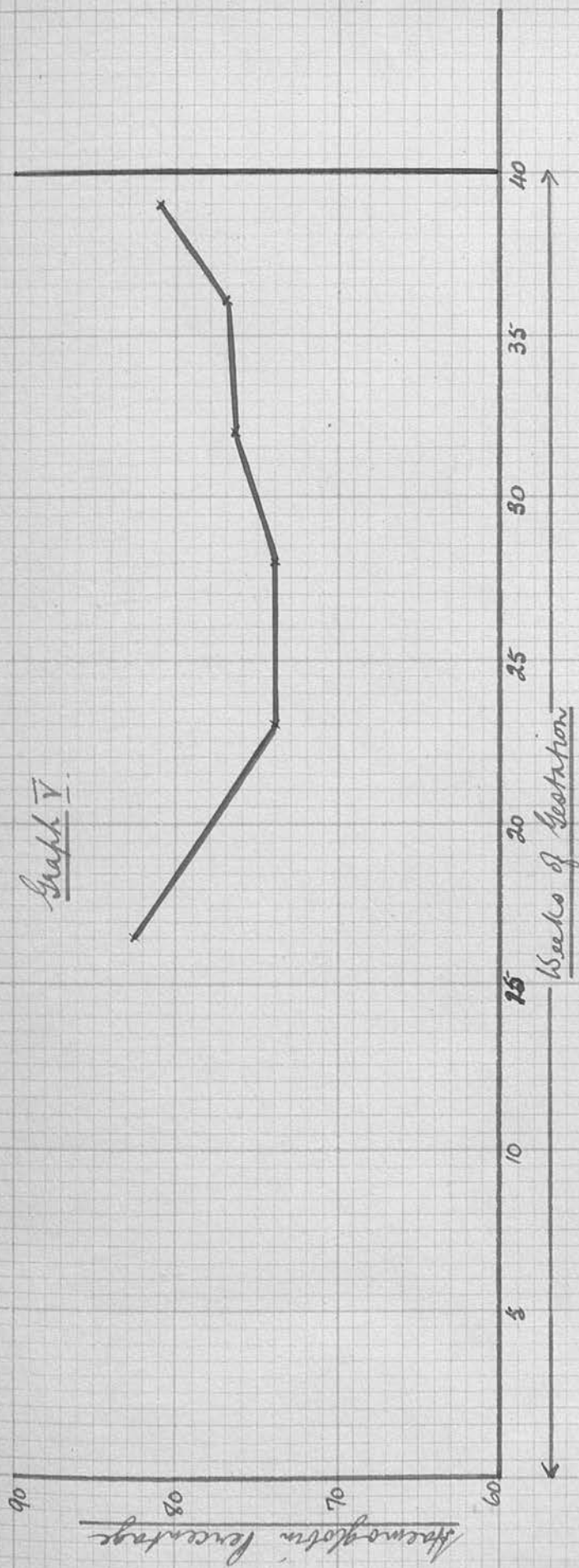
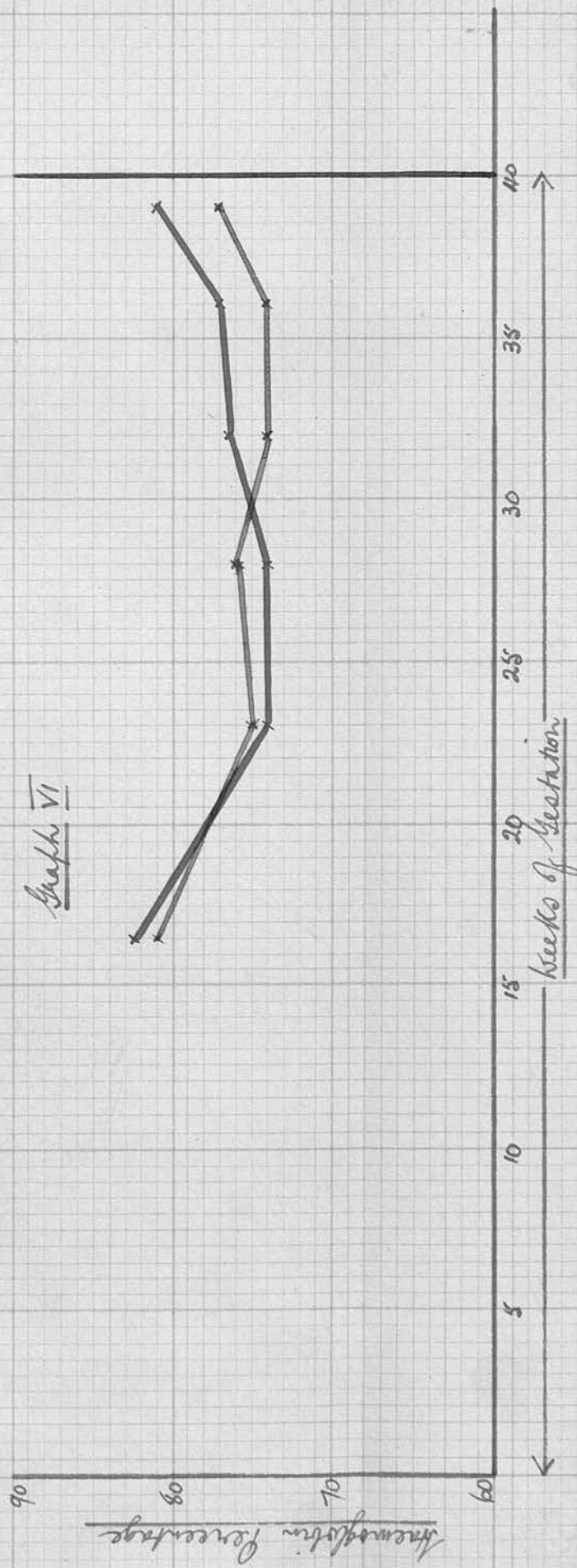
women may on occasions lead to some slight rise in haemoglobin, but is not indicative of any iron need calling for routine iron therapy.

#### Own Results of Iron Therapy in Normal Pregnancy.

There were 63 cases which could be considered normal for the whole of pregnancy and the puerperium. The haemoglobin standard of normality has already been discussed as it applies to this investigation. These cases eventually were divided into two groups :

(1) Treated Group of 26 cases, all of whom had received iron for a period of not less than 8 weeks in pregnancy and (2) Control Group of 37 who have already been considered in discussing the normal haemoglobin levels of pregnancy. These 37 formed the greater part of the cases going to compile Graph I. Altogether there were 40 cases in the group, three being derived from abnormal cases during the puerperium, who had been normal up to the time of delivery. In addition to the 26 in the treated group there were other 7 cases derived from abnormal groups in the puerperium, (e.g. Sepsis, Haemorrhage etc. after delivery) but who had been treated with iron before delivery and had shown a normal gestational period. Graph V therefore applies to the group of 33 iron treated normal cases in pregnancy. Table X shows the details from which Graph V was composed.



Graph VGraph VI

Weeks of Gestation	13 - 19	20 - 26	27 - 30	31 - 34	35 - 38	39 - 40
No. of Results	6	23	18	36	65	54
Range %	78 - 87	64 - 85	64 - 90	60 - 100	63 - 95	64 - 96
Av. Hgb. %	82.5	74	74	76.5	77	81

Number of Cases from which results were obtained = 33.

TABLE X.

The same general remarks, regarding the fall and rise of haemoglobin in pregnancy, as made in discussing the Normal Untreated group, can be made here. Considered alone it is noted that Graph V shows the same decline in haemoglobin from an initial level almost the same as that of the control group. The administration of iron therefore does not prevent what appears to be a physiological fall in the haemoglobin, due to increasing dilution with advancing pregnancy. The rise towards term has been discussed already and has been taken by certain authors to indicate the benefit derived from iron therapy. However, this same feature was seen in the control group to a limited extent.

For comparison of the 40 Control and the 33 iron-treated cases, Graph VI has been drawn. A remarkable similarity in the two curves is shown. The start of each group is very close and cannot be considered as a factor influencing the levels throughout pregnancy. Until the last trimester neither group has any advantage, but during the last few weeks the treated group shows an advantage of 3-4% haemoglobin over the untreated. Here then we have exemplified what was already deduced from the literature, namely that there is no striking advantage from the administration of iron to normal, non-anaemic women in pregnancy; the slight advantage shown at term in the treated group will be referred to again at the end of this section on/

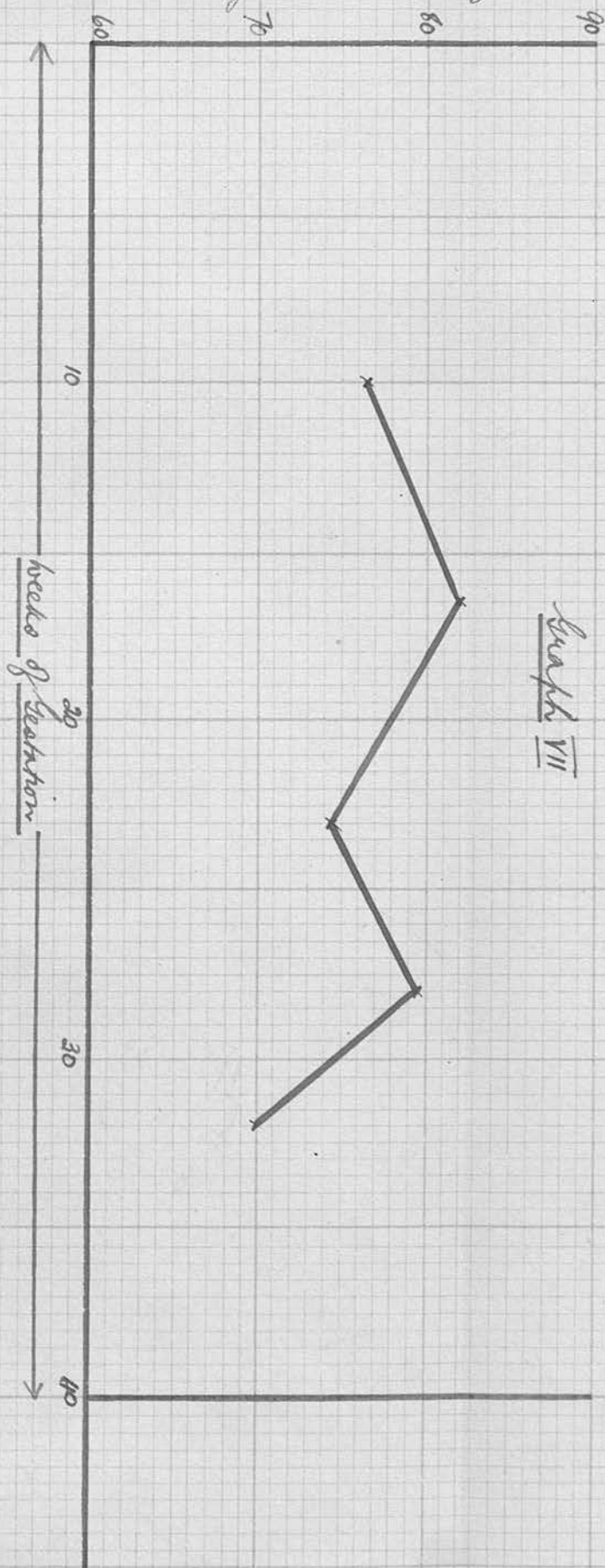


on Iron Therapy.

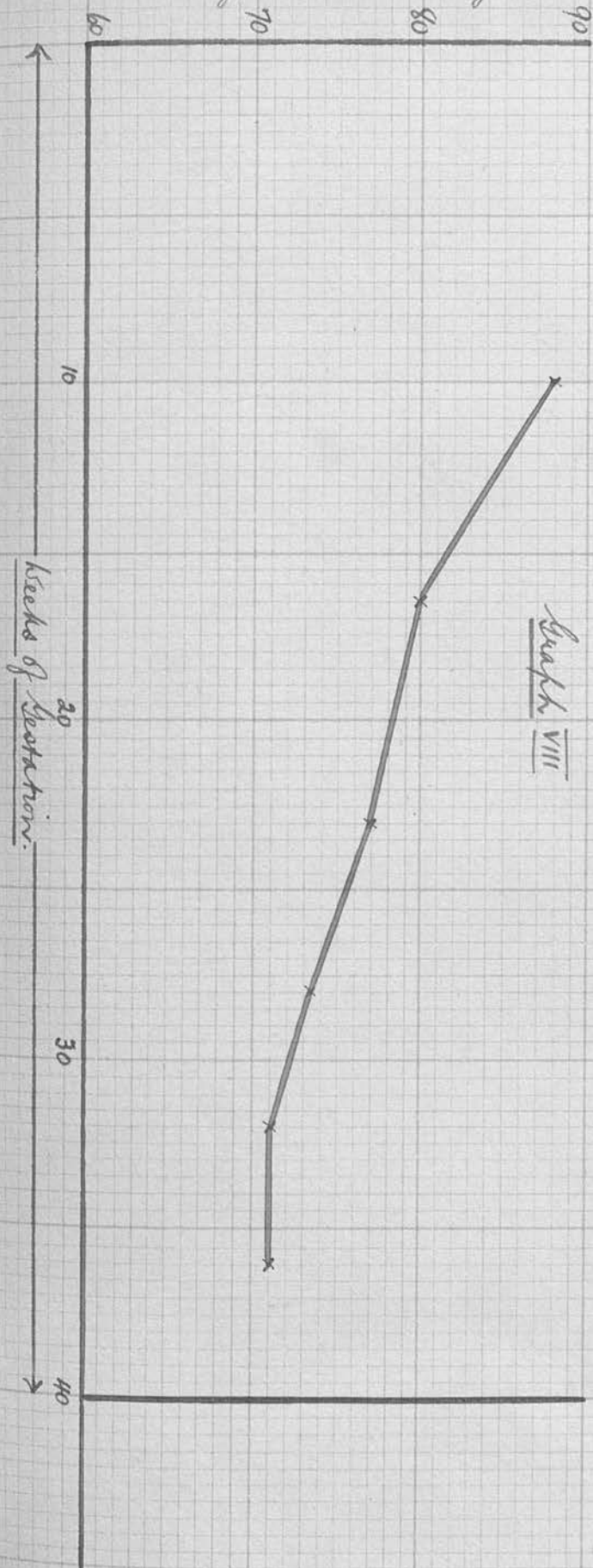
The initial haemoglobin of the two normal groups just studied is almost identical. However, these averages are taken from only a small number of cases and many of the patients were not seen for the first time until later in pregnancy. Graphs VII and VIII have been compiled from the initial haemoglobin of each case in the two groups, treated and control, respectively. The haemoglobin at the first examination has been charted at the appropriate period of gestation and then averages, for the various intervals of pregnancy, made as in previous Graphs. The details of Graphs VII and VIII are set out in Tables XI and XII.

The number of readings involved in the compilation of these two graphs are necessarily small compared with the number of readings in the graphs I and V, for the two normal groups, therefore the method of averaging lacks the same accuracy. Also figures have not been obtained in Table XI for any date after the 32nd week, since any cases seen after this date would require to be included with the control group. Even in Table XII figures are not obtainable for the last two weeks of pregnancy. The rise which has been seen formerly towards term is therefore not noticed in these graphs. Graph VIII corresponds in a general way to/

Haemoglobin Percentage



Haemoglobin Percentage



Weeks of Gestation	10 - 12	13 - 19	20 - 26	27 - 30	31 - 34	35 - 38	39 - 40
No. of Results	2	3	9	7	4		
Range of Hgb. %	75 - 78	77 - 85	65 - 82	77 - 85	65 - 77		
Av. Hgb. %	76.5	82	74.5	79.5	70		

TABLE XI.

Weeks of Gestation	10 - 12	13 - 19	20 - 26	27 - 30	31 - 34	35 - 38	39 - 40
No. of Results	3	5	5	4	6	7	
Range of Hgb. %	84 - 95	65 - 90	69 - 85	70 - 80	60 - 82	65 - 85	
Av. Hgb. %	88	80	77	73.5	71	71	

TABLE XII.



to the graph of the control group (Graph I) as might be expected since all the cases are untreated. Comparing Graph VII with Graph V the similarity at first is not so marked as that just mentioned between Graphs VIII and I. The initial haemoglobin at 10 weeks is low but may easily be due to the fact that only two cases on the lower limits of normal are involved. Otherwise the graph shows a fall from the thirteenth week until the 32nd week.

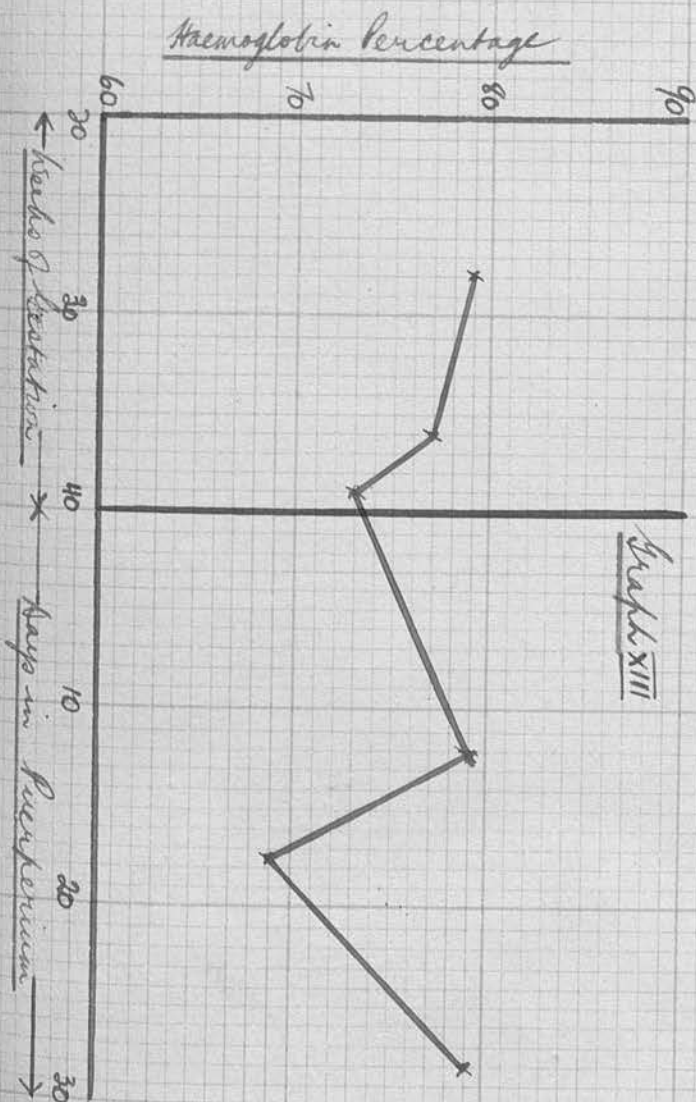
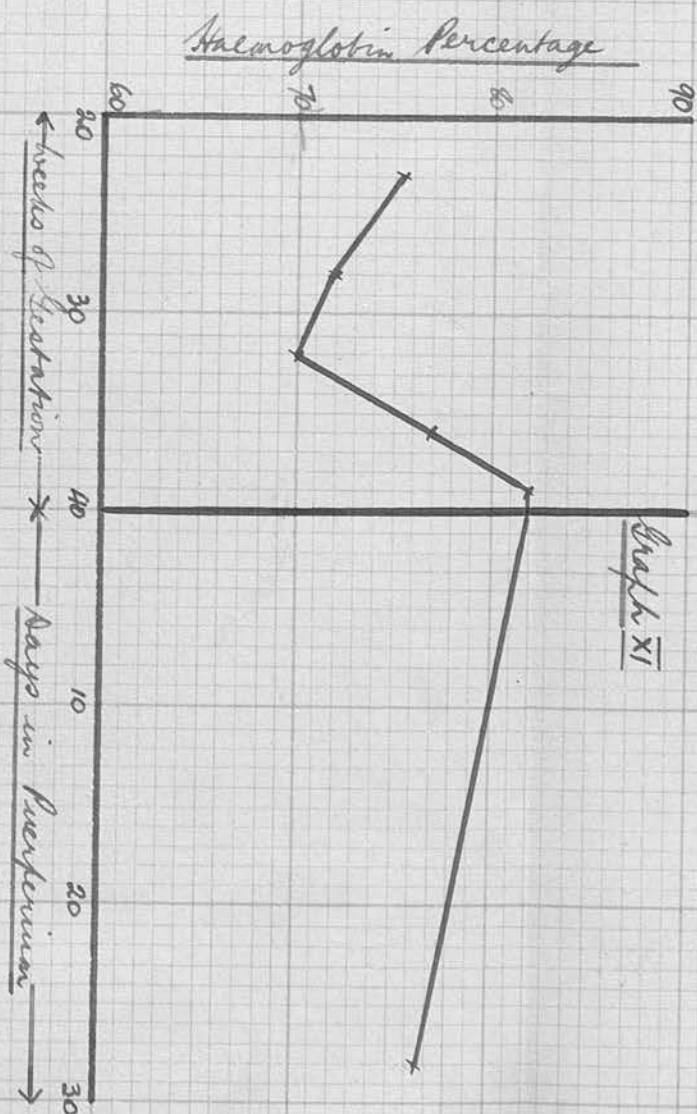
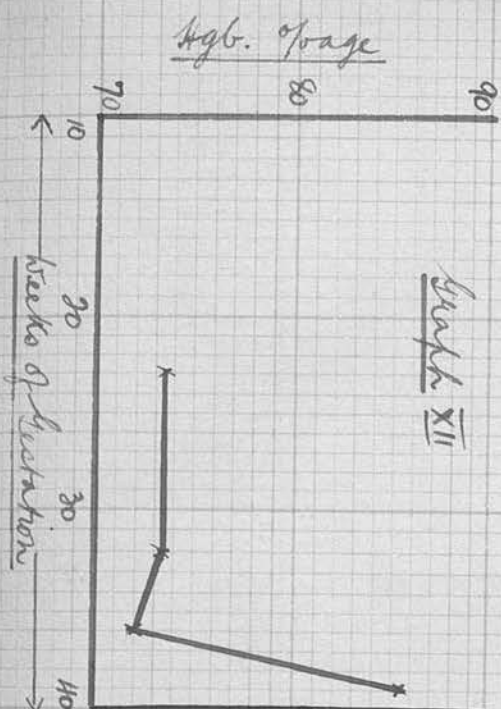
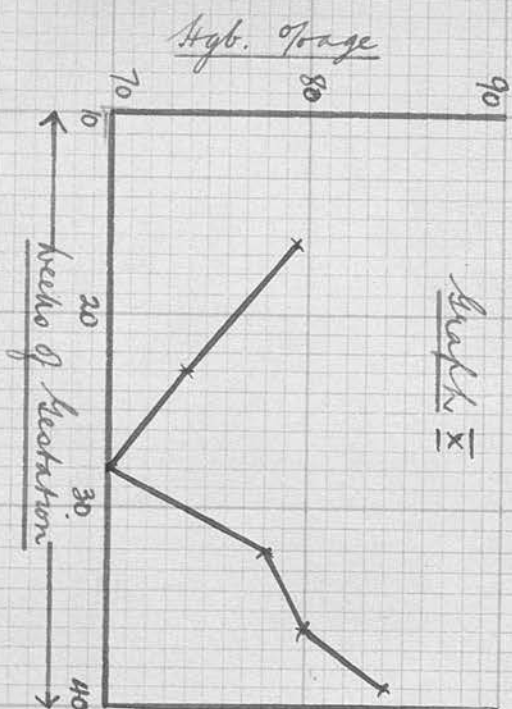
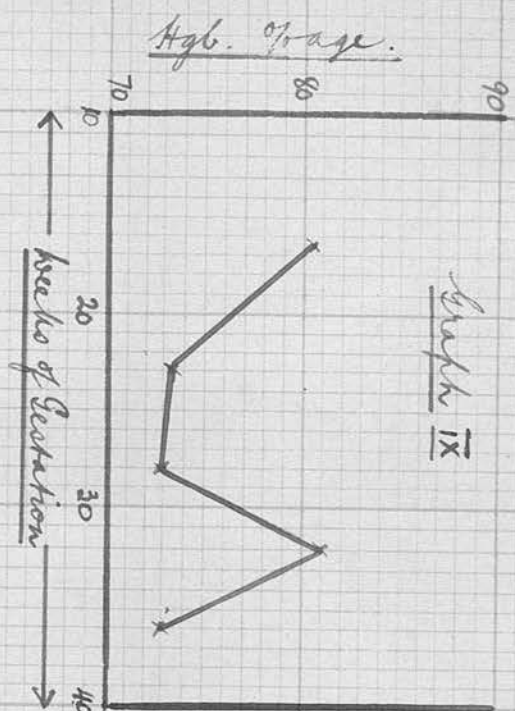
These graphs of the initial haemoglobins in the control and treated groups show that we cannot consider the initial haemoglobin as a static figure regardless of the period of pregnancy in which it is obtained. Rather does this investigation point to the fact that the duration of pregnancy is the most important single factor in deciding what the haemoglobin level will be for any case. We can also state that from this more detailed study of the initial haemoglobin levels in the two groups, neither shows any marked advantage over the other. Therefore our investigation of the effects of iron therapy are not vitiated by comparing groups which are initially dissimilar.

If the slight advantage at term, in the treated group as compared to the control group, is significant then one would expect that the duration of iron treatment would have some influence upon the level attained at any particular period of pregnancy. Not all of the treated/

treated cases at term, had received the same quantity of iron. An attempt therefore has been made to further analyse the effects of iron in normal pregnancy by charting the haemoglobin levels of each case on separate graphs after 4, 8, 12, 16 and 20 weeks of treatment. The number of results on each succeeding graph becomes smaller, as the period of treatment increases. However, no case has been included which was not treated for at least eight weeks. The same method, as previously, of obtaining averages for different periods of gestation, has been employed. Graph IX and Table XIII apply to those treated for four weeks. Graph X and Table XIV to those treated for eight weeks and so on to Graph XIII and Table XVII which apply to those treated for 20 weeks.

Graph IX shows a fall from the end of the first trimester until the period 35-38 weeks, with only one exception at the period 31-34 weeks. This corresponds in a general way to what has already been found in all the groups studied so far, whether these have been treated or not. There is no figure for the last two weeks of gestation and therefore there is no opportunity to note any change in the haemoglobin level before delivery.

Graphs X, XI and XII show the fall in haemoglobin during the second and earlier part of the third trimester, just as was found in the control and iron treated/





Time	A.P. 13-19w	A.P. 20-26w	A.P. 27-30w	A.P. 31-34w	A.P. 35-38w	A.P. 39-40w	P.P. 10-14d	P.P. 15-21d	P.P. 22-35d
No. of Results	2	5	6	8	4				
Range Hgb. %	80-81	64-80	66-84	75-94	66-84				
Av. Hgb. %	80.5	73.4	73.3	81	73				

TABLE XIII.

Time	A.P. 13-19w	A.P. 20-26w	A.P. 27-30w	A.P. 31-34w	A.P. 35-38w	A.P. 39-40w	P.P. 10-14d	P.P. 15-21d	P.P. 22-35d
No. of Results	2	2	3	6	8	4			
Range Hgb. %	79-80	70-78	65-75	73-83	71-90	74-92			
Av. Hgb. %	79.5	74	69.3	78.3	80	84			

TABLE XIV.

Time	A.P. 13-19w	A.P. 20-26w	A.P. 27-30w	A.P. 31-34w	A.P. 35-38w	A.P. 39-40w	P.P. 10-14d	P.P. 15-21d	P.P. 22-35d
No. of Results	2	2	3	6	4				2
Range Hgb. %	72-79	66-78	66-73	73-85	75-88				72-81
Av. Hgb. %	75.5	72	70	77	82				76.5

TABLE XV.

treated groups already considered. There is a marked and steep rise of haemoglobin in each of these graphs but it is difficult to see any advantage for treatment lasting longer than eight weeks. Those treated for only eight weeks show no disadvantage compared to those treated for sixteen weeks. There is however, a striking increase in the level of haemoglobin attained in these two groups (8 weeks and 16 weeks of treatment) compared to the untreated control group. One is almost convinced by these charts of the advantage of iron therapy in normal cases but the last group, shown on Graph XIII and Table XVII, which contains those treated for 20 weeks is in direct contradiction and actually shows a fall towards and at term. Admittedly the numbers in this group are very small, but one would have expected these cases to have shown a maximal rise in haemoglobin after 20 weeks of treatment. The same criticism of paucity of numbers may be brought against all of these groups, but the impression conveyed by this study, is that the factor of most importance in deciding the haemoglobin level in any patient, is the period of gestation. The number of readings as applied to the first six weeks of the puerperium are too small to enable any deductions to be drawn from them as regards the effect of administering iron.

The conclusion to be drawn is that the Iron treated/

treated cases show a 3-4% increase at term in the haemoglobin level, as compared to the control group. Whether this rise is of significance is doubted in view of the fact that iron therapy does not alter the natural fall and rise of haemoglobin as seen in pregnancy. At the end of the complete discussion on iron therapy, the significance of iron in pregnancy will again be discussed.

2. Anaemia. The results of administering iron to patients with a hypochromic anaemia in pregnancy are not difficult to assess, since every investigation is in agreement that iron leads to a favourable response. The true nature of the anaemia arising in pregnancy and its relationship to the other commonly found hypochromic anaemia of women will be fully discussed when all the results of our investigation have been considered.

Mettier et al<sup>67</sup> (1933) assume the identity of anaemia in pregnancy and the idiopathic hypochromic anaemia of adult women and show the response to iron in 10 cases, one of whom was pregnant at the time of treatment. Strauss<sup>88</sup> (1934) gave convincing evidence in 30 cases, with hypochromic anaemia in pregnancy, that iron produces a rise in the haemoglobin towards normal levels. Also Bethell<sup>5</sup> (1936) showed that microcytic anaemia in pregnancy responds to iron therapy. The/



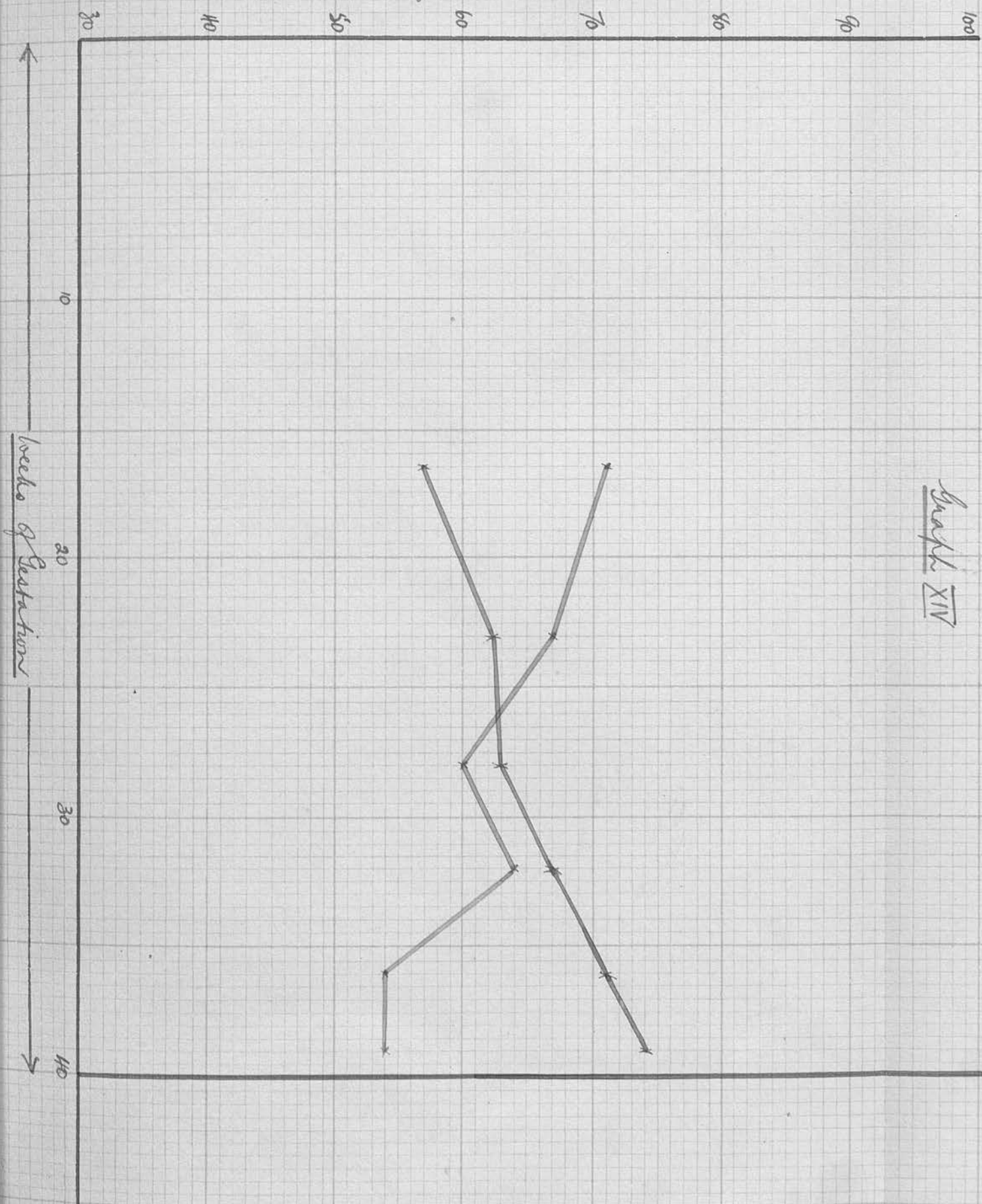
The response, however, in pregnancy is not to normal levels since hydraemia also exists. Labate<sup>49</sup> (1939) showed a response in an iron treated group of 325 patients whose average haemoglobin rose from an initial reading to 9.56 Gms. to 11.61 Gms. at delivery. The response to iron of microcytic hypochromic anaemia in pregnancy is therefore quite clearly established from the literature.

Something has already been said regarding the cases of anaemia in pregnancy reported in this series of 104 cases. It was seen that one group of five cases was untreated and served as a control for the group of five cases who received treatment. The individual graphs (III and IV) were presented earlier and commented upon, also the possible time of incidence of the anaemia in pregnancy. Graph XIV, which is Graphs III and IV superimposed, is inserted here and shows a striking contrast in the two groups. It will be noted that the untreated group started with an advantage in the haemoglobin level. This advantage was more than completely reversed at the time of delivery. Even in this small group therefore there is no reason to doubt the efficacy of iron as a therapeutic agent in restoring the haemoglobin level of anaemic women in pregnancy. Confirmation is also added to the finding of others reported above, that the level of haemoglobin in the treated group does not reach/

71 a.

Graph XIV

Haemoglobin Percentage.



reach non-pregnant levels of normality but is modified by the presence of the hydraemia of pregnancy.

### Routine Administration of Iron in Pregnancy.

Many authors consider that it is justifiable to administer iron routinely to pregnant women (Evans<sup>29</sup> (1937)). Corrigan and Strauss<sup>17</sup> (1936) conclude that the giving of iron would largely prevent the hypochromic anaemia of pregnancy, while Adair et al<sup>2</sup> (1936) believed the administration of iron was more effective in preventing anaemia in pregnancy than in curing it. The incidence of pregnancy anaemia, however, is probably small, (Boycott<sup>8</sup> (1938)) except in the very poor classes showing a marked nutritional anaemia among adult females (Davidson et al<sup>18</sup> (1935)), and it seems unjustifiable to administer iron as a routine, when a simple haemoglobin estimation would act as an indicator towards the truly anaemic, who could be further investigated regarding the red cell count and colour index and then treated with iron when necessary. Bethell<sup>5</sup> (1936) would appear to go too far in recommending that all cases with a lowered colour index should be given iron, regardless of the haemoglobin level, since there is no indication as to the colour index which he considers normal. Lundholm<sup>56</sup> (1939) defined hypochromic anaemia, as an anaemia with colour index below 0.75 and it is unlikely that a patient with 70% haemoglobin/



haemoglobin (Sahli), which is the level of anaemia adopted by Bethell, would show a colour index lower than 0.75 or even 0.8, which is more generally accepted than Lundholm's figure, as the lower normal figure for the colour index.

The results of McGeorge<sup>61</sup> (1935) and Corrigan and Strauss<sup>17</sup> (1936) indicate an advantage for the treated groups in the early puerperium, and the former results have been obtained after eliminating cases with post-partum haemorrhage from both treated and control groups. These authors see in their results the justification for using iron prophylactically, but again the criticism may be advanced that their results are affected by the inclusion of some anaemic cases. These cases could be found out by routine haemoglobin estimation, but do not serve as an excuse for subjecting normal individuals to iron therapy for no result to themselves.

Summary. This topic of Iron Therapy in Pregnancy may be summarised by saying that the reduction of haemoglobin as a result of hydraemia is not affected by iron therapy and that the blood cannot be restored to normal non-pregnant levels by iron. The value of iron in cases of hypochromic anaemic in pregnancy is undisputed. There seems to be no justification for routine iron therapy in pregnancy, but routine haemoglobin estimations are indicated as part of ante-natal care.

## B. Puerperium.

The normal behaviour of the blood in the puerperium has already been considered. It is now intended to consider the influence of iron therapy upon normal cases and anaemic cases so far as altering the blood picture in the puerperium is concerned. We have just mentioned that McGeorge<sup>61</sup> (1935) and Corrigan & Strauss<sup>17</sup> (1936) reported an advantage in the early puerperium for a group of treated cases compared to an untreated group in pregnancy, but the criticism was advanced that these groups may have included some anaemic cases. We may therefore ask, what effect has the administration of iron, in pregnancy, in normal cases, upon the haemoglobin level in the puerperium?

Figures are obtainable in the literature to compare the normal groups with and without iron, yet the effects of blood loss at parturition cannot be wholly assessed and the results must be affected by this blood loss. However, in a large series, if obvious cases of severe haemorrhage are excluded and also other causes of anaemia e.g. sepsis, then the two groups may be comparable. 29 control and 30 iron treated cases were followed by Mackay<sup>62</sup> (1931) into the puerperium. These cases all started the investigation in pregnancy with haemoglobin over 70%. The total period of observation of the Controls and the treated cases was about 190 days in each group, the treated cases receiving iron during the whole of this period/

period. The figures for the control group at the start of the investigation and at the end (146 days after delivery) were 78.4% and 84.1% respectively. The corresponding figures for the treated group (136 days after delivery) were 78.3% and 88.8%. Davis and Walker<sup>23</sup> (1934) found an incidence of 63% of anaemia in their studies, but this has been shown (cf. Incidence of Anaemia) to be too high and must include many merely showing hydraemia. The results of giving iron in this group may therefore be considered, up to a point, to show the effect of iron in normal pregnancy upon the blood in the puerperium. The treated group are said to have had a speedier recovery in the puerperium than the untreated group. On the 8th day after delivery Richter et al<sup>82</sup> (1934) found that a treated group of 38 pregnant women had an average haemoglobin of 88.5% as against the 61 untreated with an average of 83%. Again Irving<sup>44</sup> (1935), whose 60 anaemic cases may be criticised like those of Davis and Walker, showed an advantage for the treated cases on the first day after delivery of 73.9% as against 67% for the untreated. Each group started with an average of 67% in pregnancy. The results of Corrigan and Strauss<sup>17</sup> (1936) in a selection of normal cases (no haemorrhage or sepsis in pregnancy or puerperium) from 200 investigated, showed that the treated group at the end of one week from delivery/



delivery had an average haemoglobin of 85% as against 75% in the untreated group. The initial haemoglobin of each group was comparable, namely 73% and 75% respectively. Further only 5 in the treated group were below 75% after one week, while there were 45 in the untreated group and in this latter group also 24 below 70% as against none in the treated group. Even allowing for a certain percentage with anaemia in pregnancy the results are strikingly in favour of iron therapy before delivery. Smallwood<sup>84</sup> (1936) reports a slight advantage in the puerperium for the 59 treated cases as against the 106 untreated. The treated cases in pregnancy of Gottlieb and Strea<sup>37</sup>n (1939) are reported to return rapidly to normal after delivery, and the assumption is that the untreated group do not return to normal so quickly. The facts however as presented fail to convince one that the return is so rapid in the puerperium as the authors try to convince us it is.

Although Mackay's figures are the only ones which seem to apply solely to patients who were not anaemic in pregnancy, yet the results of the others are so similar - and certainly did not contain so high a percentage of anaemic cases as was thought by the authors - that they may be taken as added confirmation of the effects of iron therapy upon the haemoglobin in the puerperium. When Mackay compared larger groups each containing some anaemic cases, but treated similarly/

similarly to the two groups above, the results were of the same order as those already quoted. It might be objected that Mackay's results were obtained after iron therapy which was continued during an average of 136 days in the puerperium whereas the other author's figures were obtained from cases treated only in pregnancy. This is true, but we find no similar investigation in the literature to that of Mackay and can only compare her results with those of others receiving iron in pregnancy only. Labate<sup>49</sup> (1939) gave iron to patients for the period of their stay in hospital after their confinement, but concluded that the period of observation was too short in order to obtain results and therefore this does not help us to a further understanding of Mackay's results i.e. whether the response is due mainly to iron in the puerperium or, like the others quoted, the result of iron in pregnancy.

If the results of iron therapy are favourable to groups of patients - mostly not anaemic - it can be assumed that the results will be favourable to a greater extent in anaemic cases. Fullerton's results<sup>33</sup> (1936) which were obtained with women showing a high incidence of anaemia, bear out this expectation since he shows that the percentage increase in the puerperium over the pregnancy level of haemoglobin is greater in those with a low initial haemoglobin. This applies to both/

both treated and untreated groups, but the former(54) show an average rise at the end of one year from parturition of 10% as against a rise of 8.6% in the untreated group of 97 cases.

#### Our Results of Iron Therapy on the Puerperal Blood.

Of the investigations mentioned in our study of the literature it was seen that Mackay continued the administration of iron during pregnancy and the puerperium. Most of the other results with which hers could be compared, only administered the iron during pregnancy and then noted any advantages therefrom in the puerperium. Only Labate was recorded as having administered iron during the puerperium but the period of administration during the stay in hospital was found to be too short to note any results.

The results of the normal control group of 21 Patients, who showed no anaemia either in pregnancy or the puerperium and received no iron therapy, have been recorded graphically in Graph II.

In order to study the effects of iron therapy fully the remainder of the 63 normal cases were eventually placed in three groups:-

1. Treated with iron during pregnancy and the six weeks following delivery (11 cases).
2. Treated with iron during pregnancy and receiving no treatment in the puerperium (15 cases).

3./



3. No treatment in pregnancy but iron for six weeks in the puerperium. (16 cases)

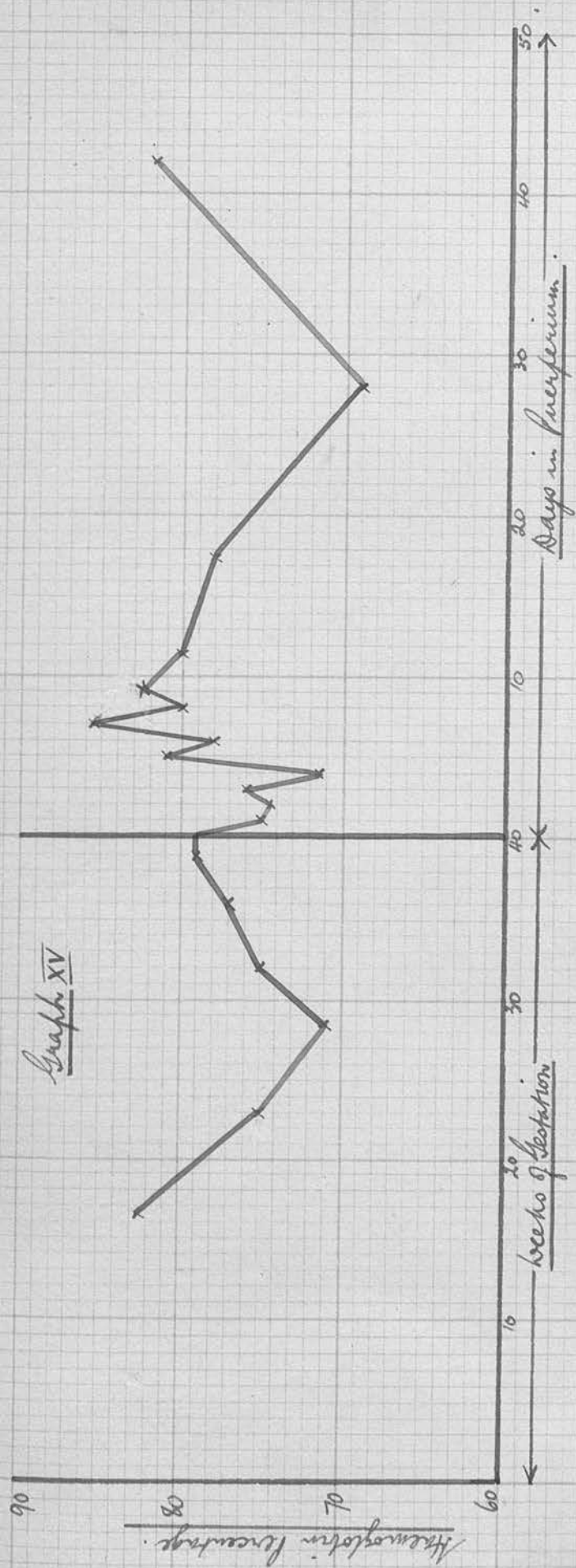
The first group is detailed in Table XVIII and Graph XV; the second group in Table XIX and Graph XVI; while the third group is detailed in Table XX and Graph XVII. Graph XVIII is inserted in order to facilitate a comparison of these three groups with the normal already shown in Graph II.

See TABLES XVIII, XIX and XX.

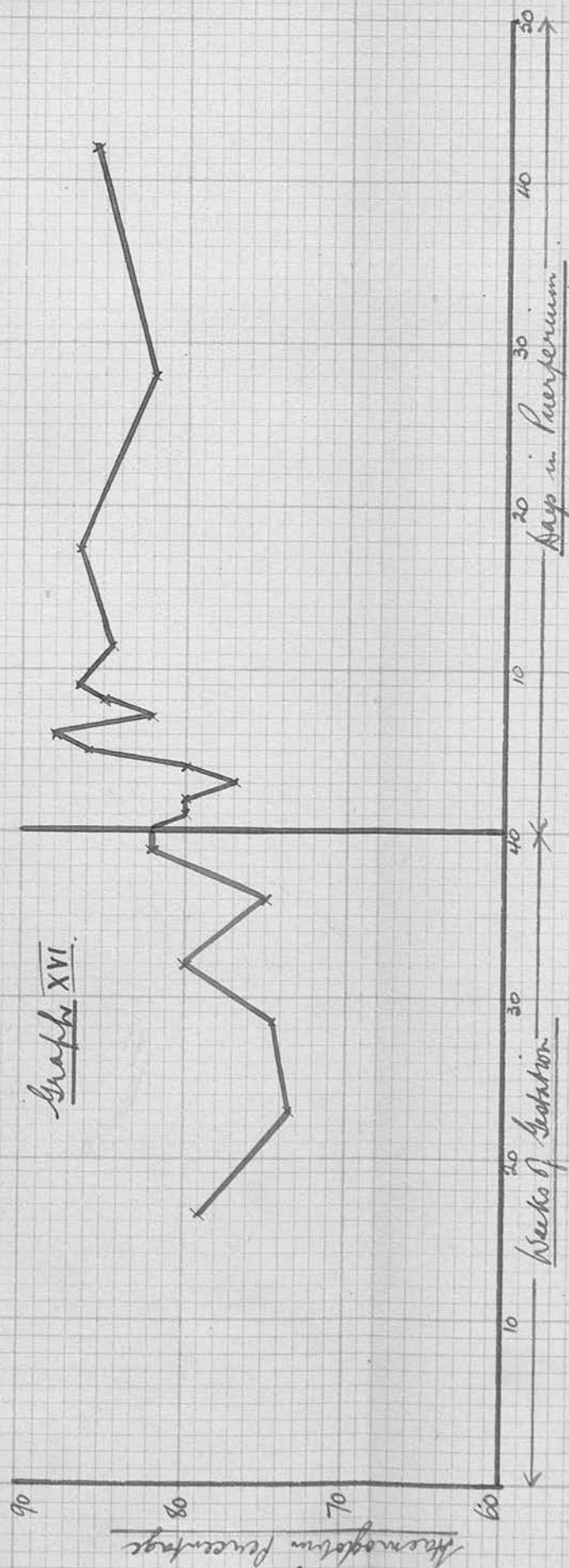
The first group which received the prolonged iron therapy would naturally be expected to show the greatest benefit if any were to be derived from treatment. The second group was planned to show what effects iron in pregnancy might have upon the puerperium and serves as a comparison with most of the recorded results in the literature. The third group was planned to show the results of iron therapy in the puerperium alone and thus to enable us to ascertain more exactly when the effects of iron administration are most likely to be made manifest, if at all, in a normal group of cases.

Reference to the figures for each group will show that after delivery the haemoglobin level fluctuates for the first 3 or 4 days and by this time has usually reached its lowest figure. After this time, until the patient's discharge or return to some duty at the end of a fortnight, there is no group which shows a fall in/

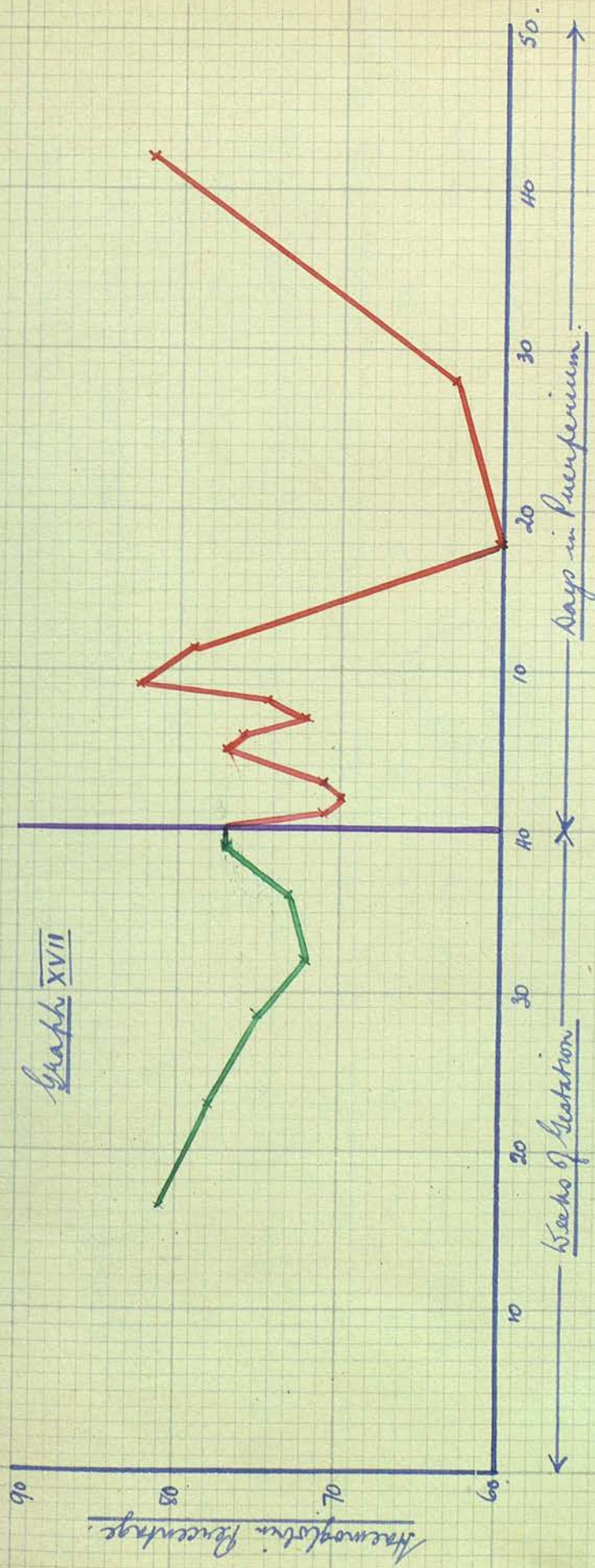
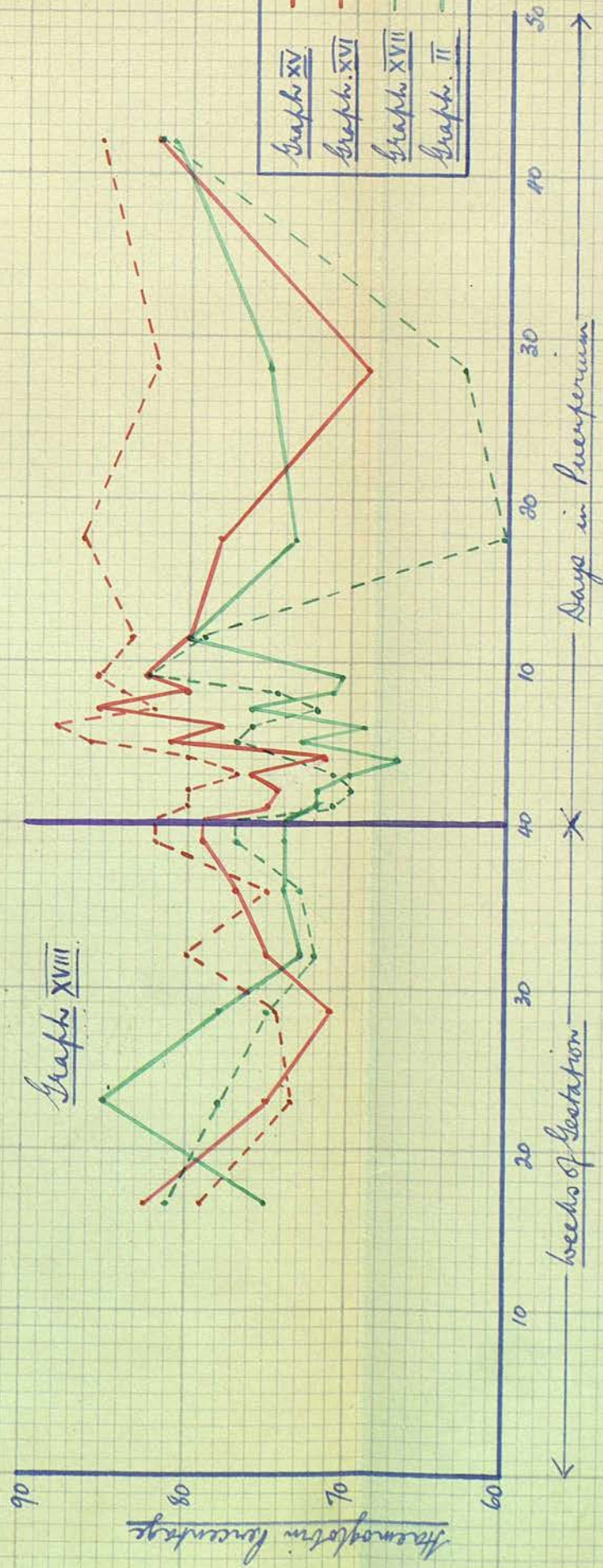
Graph XV



Graph XVI





Graph XVIIGraph XVIII



Weeks of Gestation	13 - 19	20 - 26	27 - 30	31 - 34	35 - 38	39 - 40							
No. of Results	2	8	6	11	19	17							
Range %	80 - 85	65 - 83	64 - 75	68 - 87	63 - 94	64 - 93							
Av. Hgb. %	82.5	75	71	75	77	79							
Days of Puerperium.	1	2	3	4	5	6	7	8	9	10-14	15-21	22-35	36-50
No. of Results	15	9	7	6	5	5	2	5	2	12	4	3	12
Range %	63-90	60-94	56-95	63-80	75-93	55-92	84-87	66-100	79-86	67-101	75-83	67-73	65-105
Av. Hgb. %	75	74.5	76	71.5	81	78	85.5	80	82.5	80	78	69	82

Number of Cases from which results were obtained = 11.

TABLE XVIII.

Weeks of Gestation	13 - 19	20 - 26	27 - 30	31 - 34	35 - 38	39 - 40
No. of Results	2	7	6	13	19	22
Range %	78 - 80	64 - 85	65 - 82	67 - 100	68 - 85	68 - 96
Av. Hgb. %	79	73.5	74.5	80	75	82

Days of Puerperium	1	2	3	4	5	6	7	8	9	10-14	15-2	22-35	36-50
No. of Results	24	14	9	7	5	6	2	8	4	15	5	3	12
Range %	55-98	60-98	63-98	53-98	75-99	75-101	78-86	70-110	80-90	73-103	65-102	74-89	70-100
Av. Hgb. %	80	80	77	80	86	88	82	85	86.5	84.5	86.5	82	85.5

Number of Cases from which results were obtained = 15.

Weeks of Gestation	13 - 19	20 - 26	27 - 30	31 - 34	35 - 38	39 - 40
No. of Results	9	12	11	14	20	25
Range %	73 - 90	69 - 85	70 - 85	60 - 89	63 - 85	62 - 96
Av. Hgb. %	81	78	75	72	73	77

Days of Puerperium	1	2	3	4	5	6	7	8	9	10-14	15-21	22-35	36-50
No. of Results	22	14	12	2	7	6	4	2	7	16	1	1	12
Range %	60-88	58-87	50-85	92-94	62-91	69-81	62-88	66-83	70-87	65-93	60	63	72-94
Av. Hgb. %	71	70	71	79.3	77	76	72	74.5	82.5	79	60	63	82

Number of Cases from which results were obtained = 16.



in the haemoglobin as compared to the level at delivery. From this point the graphs appear to be somewhat variable, but here it must be admitted, the opportunity for frequent readings were few and therefore the averages are made from only a few results. However, the general trend is the same in each group, with a fall between the end of the second week in the puerperium and the final reading at the end of six weeks. At this last reading, which was deliberately taken as near the completion of six weeks and in as many patients as possible, we note that in all three groups there has been a return of the haemoglobin towards normal standards for the non-pregnant. The final figures in each group are remarkably close to each other and to the corresponding figure for the control group. Only the second group could be said to show any slight advantage. In view of the fact that one would have expected this in group one, if at all, it seems doubtful if this slight advantage is significant. It seems more likely that it has so happened, that group two has included a high percentage of patients in the upper limits of normality, thus accounting for the slight advantage shown also in pregnancy.

The conclusion, therefore, reached from this study of iron treated groups and their comparison with a normal control group, is that the administration of iron to normal non-anaemic women, either in pregnancy or the puerperium or during both these periods, fails to/

to show any advantage to the treated groups as compared with an untreated group of normal non-anaemic women. In each group and in the control group care was taken to exclude any patient who showed more than an average blood loss at parturition. This standard excluded women whose blood loss could not be called a true post-partum haemorrhage, but whose blood loss was nevertheless estimated clinically to be more profuse than normal.

Iron Therapy and its effect upon the Puerperal Recovery in Anaemic Women.

The patients who were classed as showing anaemia in pregnancy, were considered previously in so far as the results of iron therapy in pregnancy were concerned. These patients, it will be remembered, fell into two groups of 5 each, the one group treated and the other group untreated (Graph XIV). However, not all of these had a normal delivery and a normal puerperium, so that only three patients are available for compiling Graph XIX and Table XXI and only four for Graph XX and Table XXII. All the cases in both groups were given iron in the puerperium with the exception of one case in the iron treated group in pregnancy. As this case showed no disadvantage compared to the other two iron treated in pregnancy, it has been included with the other two in the graph. These two groups therefore show/

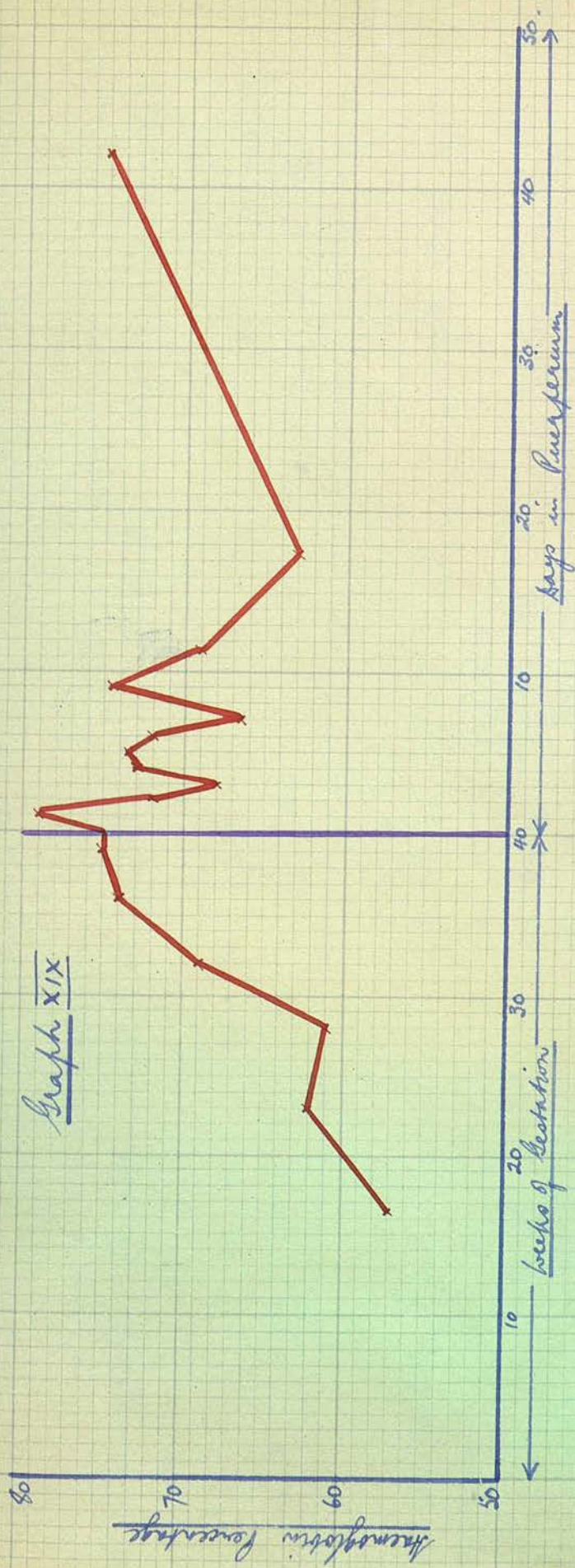
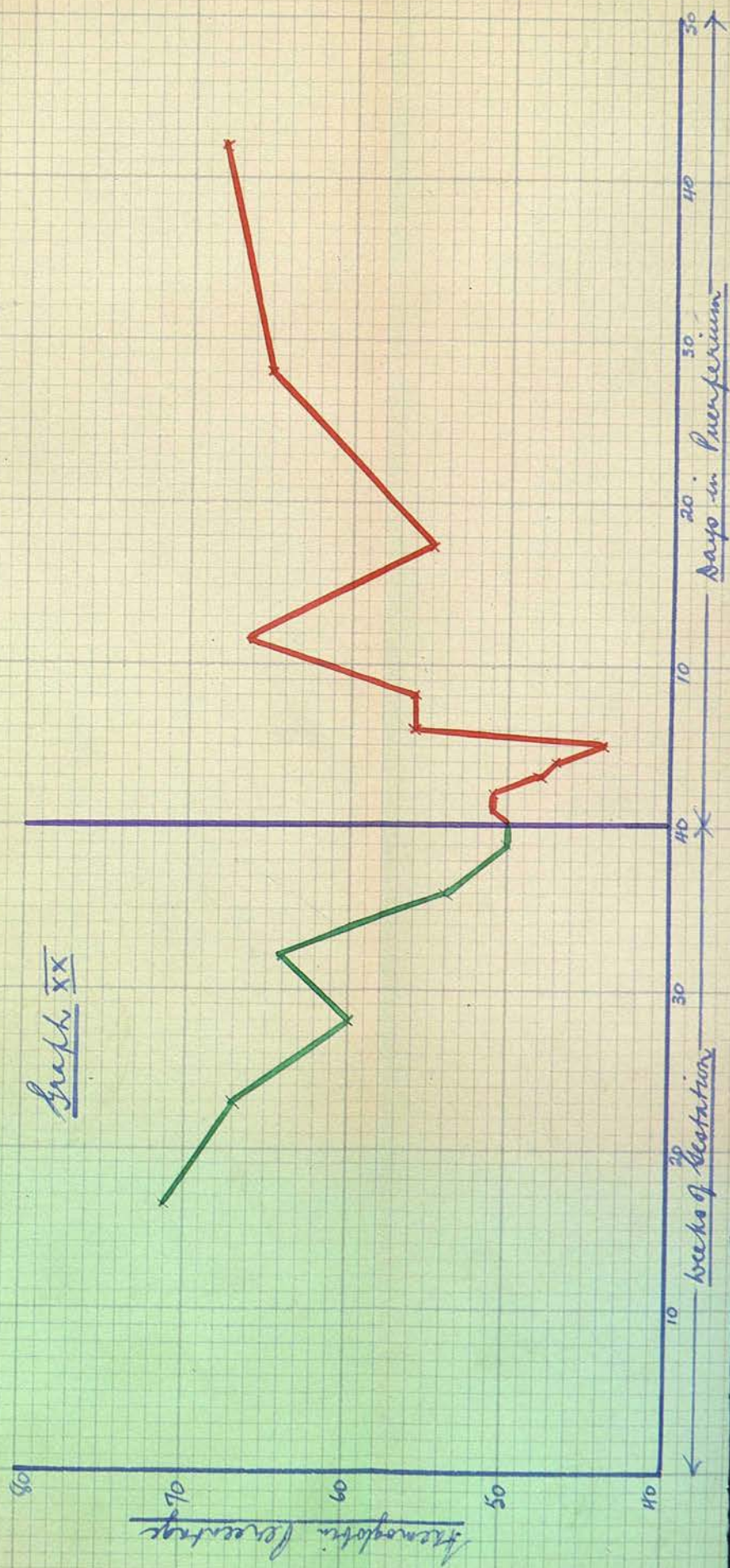
show mainly the effect of iron given in pregnancy upon the blood in the puerperium, in anaemic patients.

See TABLES XXI and XXII.

These two groups are rather difficult to compare in the puerperium since the iron treated in pregnancy started with a decided advantage after labour, over the untreated group. The corresponding figures for the treated and untreated at labour are 75 and 50 per cent. At the end of six weeks after delivery the iron treated in pregnancy have an average of 75% haemoglobin as against 68% in the untreated pregnancy group. Both groups have failed to reach normal levels at the end of six weeks. The recovery of the untreated in pregnancy has been more rapid in the puerperium than that of the treated group. This is in accordance with the findings of Fullerton who reported a greater rise in haemoglobin for the group having the lowest initial haemoglobin.

The effect of iron in pregnancy would therefore appear to be to enable patients who have been anaemic to return towards normal levels of haemoglobin more quickly in the puerperium, than is the case with the untreated anaemic group in pregnancy. This latter group, however, show a greater percentage rise of haemoglobin in the six weeks after delivery and by this time are rapidly overtaking the group which had



Graph XIXGraph XX



Weeks of Gestation	13 - 19	20 - 26	27 - 30	31 - 34	35 - 38	39 - 40
No. of Results	2	4	3	3	5	6
Range %	54 - 60	55 - 74	50 - 73	65 - 78	70 - 78	70 - 87
Av. Hgb. %	57	62	61	69	74	75

Days of Puerperium	1	2	3	4	5	6	7	8	9	10-14	15-21	22-35	36-50
No. of Results	3	2	1	2	2	1	2	-	4	4	1	-	3
Range %	59-93	55-80	68	73	65-82	72	65-68	-	67-82	60-81	63	-	72-80
Av. Hgb. %	79	72	68	73	73.5	72	66.5	-	74.5	69	63	-	75

Number of Cases from which results were obtained = 3.

TABLE XXI.

Weeks of Gestation	13 - 19	20 - 26	27 - 30	31 - 34	35 - 38	39 - 40
No. of Results	1	1	1	2	6	7
Range %	71	67	60	58 - 70	45 - 68	43 - 57
Av. Hgb. %	71	67	60	64	54	50

Days of Puerperium	1	2	3	4	5	6	7	8	9	10-14	15-21	22-35	36-50
No. of Results	5	4	3	4	1	4	-	3	-	6	2	6	5
Range %	43-60	44-60	40-59	39-53	44	48-63	-	50-60	-	57-71	55-56	60-67	60-72
Av. Hgb. %	51	51	48	47	44	56	-	56	-	66	55-5	65	68

Number of Cases from which results were obtained = 4.



a decided advantage at labour. This difference in rate of response to iron therapy in the puerperium is doubtless due to the relative lack of iron in each group and in direct proportion to the magnitude of the iron lack. The beneficial effect of iron both in pregnancy and the puerperium in anaemic cases is therefore not in doubt.

#### Discussion on Iron Therapy.

The results of administering iron either in pregnancy or the puerperium or both has led to no appreciable result as judged by the normal control group. This is contrary to what was already discovered from a study of the literature.

It was already shown in an earlier section that there was a definite return towards normality of the blood during the puerperium. The changes which occur early in the puerperium are probably due to reduction of hydraemia and not to haemotopoiesis. A definite steady rise in the haemoglobin may not begin until six weeks after delivery according to some authors, while others believe that a return to normal may be delayed some months. We have shown that at the end of six weeks a definite step towards normality has occurred, although we cannot say just how long complete recovery might take. The red blood corpuscles have been shown to return to normal figures more quickly than the haemoglobin/

haemoglobin, therefore it seems that at some stage there is present in the puerperium a hypochromic anaemia. Theoretically then, it appears that administering iron, to normal patients showing this physiological hypochromic anaemia, might result in advantages to the treated patients. If treated in pregnancy we might assume that the iron was stored - since not required by these normal patients in pregnancy - and made quickly available in the puerperium. If treated in the puerperium the iron would act as it does in any hypochromic anaemia. However, this view of the effect of iron administration upon the puerperal blood, presupposes a real iron lack in the puerperium. From our own results showing no advantage for iron therapy there would appear to be no iron shortage.

Turning again to the literature we find support of this view in the work of Oberst and Plass<sup>73</sup> (1936) who showed that the red blood cells at the time of delivery contained an increase of 7% of haemoglobin over the non-pregnant level, despite the reduction in the amount of haemoglobin per 100 ccs. of blood. This would not appear to indicate that there was any iron shortage. The effect of reduction of plasma volume in the first ten days or so of the puerperium would be expected to produce a concentration of cells and haemoglobin even in the absence of haematopoiesis. None of the results in the literature show that the concentration/

concentration of haemoglobin rises in normal untreated cases in the early days of the puerperium although this is the rule with the red blood corpuscles. What happens in the puerperium to the extra 7% of haemoglobin in each red cell at the time of delivery?

Should a strictly normal case present a rise in haemoglobin after the reduction of the hydraemia with a gradual fall to normal non-pregnant levels, while the cells are slowly regaining their normal size and haemoglobin content during the later puerperium?

If the answer to this latter question be in the affirmative then we must assume that the results presented here and the results of the authors quoted earlier in order to show the normal behaviour of the puerperal blood are vitiated either by the inclusion of many really anaemic (which we have tried to avoid in our considerations) or the inclusion of cases of severe puerperal blood loss (which was also excluded as carefully as possible) (cf. Fullerton<sup>33</sup> (1936)). All the facts seem to point to a slower return of the haemoglobin than of the red blood cells to normal in the Puerperium and some explanation of this reduction of haemoglobin must be sought, since each red cell at delivery has been shown to possess an increased amount of haemoglobin.

The normal process of red cell destruction and Katabolism of iron from liberated haemoglobin must go on as usual and in addition the extra 7% of haemoglobin from/



from each red cell must be speedily lost as the cell returns to its normal, non-pregnant size. This would apparently have the effect of liberating a plentiful supply of iron for new haemoglobin production and yet it is the haemoglobin which lags behind the red cells in the return to normal. Two possibilities seem to exist (a) That there is an increased excretion of iron in the puerperium and/or (b) Some interference of a temporary nature with the normal iron cycle in the body.

(a) The work of McCance and Widdowson<sup>59</sup> (1937) on iron metabolism has indicated that the human body probably satisfies its need for iron by controlled absorption rather than by altered excretion. Therefore it would seem anomalous that in the presence of an iron need to restore the haemoglobin level to normal, the body should excrete the extra iron in the Puerperium which has been derived from the break down of the blood cells which at delivery contained an extra 7% of haemoglobin. There are no experiments that we can find in the literature to indicate any alteration in iron metabolism in the puerperium, therefore this seems an unlikely explanation, that there is increased iron excretion.

(b) This again is no more than a hypothesis to try and explain the findings in the literature which even apart from the findings of Oberst and Plass of an increased/

increased haemoglobin content for the red cells at delivery, show an unexplained slow return to the haemoglobin to normal without an apparent iron shortage. What the nature of this supposed interference with the iron cycle could be is difficult to understand. Is it merely a delay in making the iron derived from the Katabolism of haemoglobin available for the haematopoietic centres? This seems unlikely in view of the reserve powers of the liver to break down haemoglobin. Is it due to an alteration of the haemoglobin itself comparable to the alteration found in the foetal haemoglobin? This too seems unlikely. If either of these two explanations were true than it might explain the good response obtained by giving iron either before or after delivery, as has been reported by certain authors, since the iron given in pregnancy would be stored ready for immediate haematopoiesis while that given in the puerperium would be quickly absorbed and available for haemoglobin formation. That such a beneficial result is to be expected where there is an iron lack in the puerperium seems to be borne out by a small number of cases which have been investigated and which are now presented in the development of this discussion.

There were 12 out of the 104 cases who showed what we believed to be an excessive blood loss at parturition. 7 of these received iron before delivery and 5 had no ante-natal iron therapy. One of the treated/

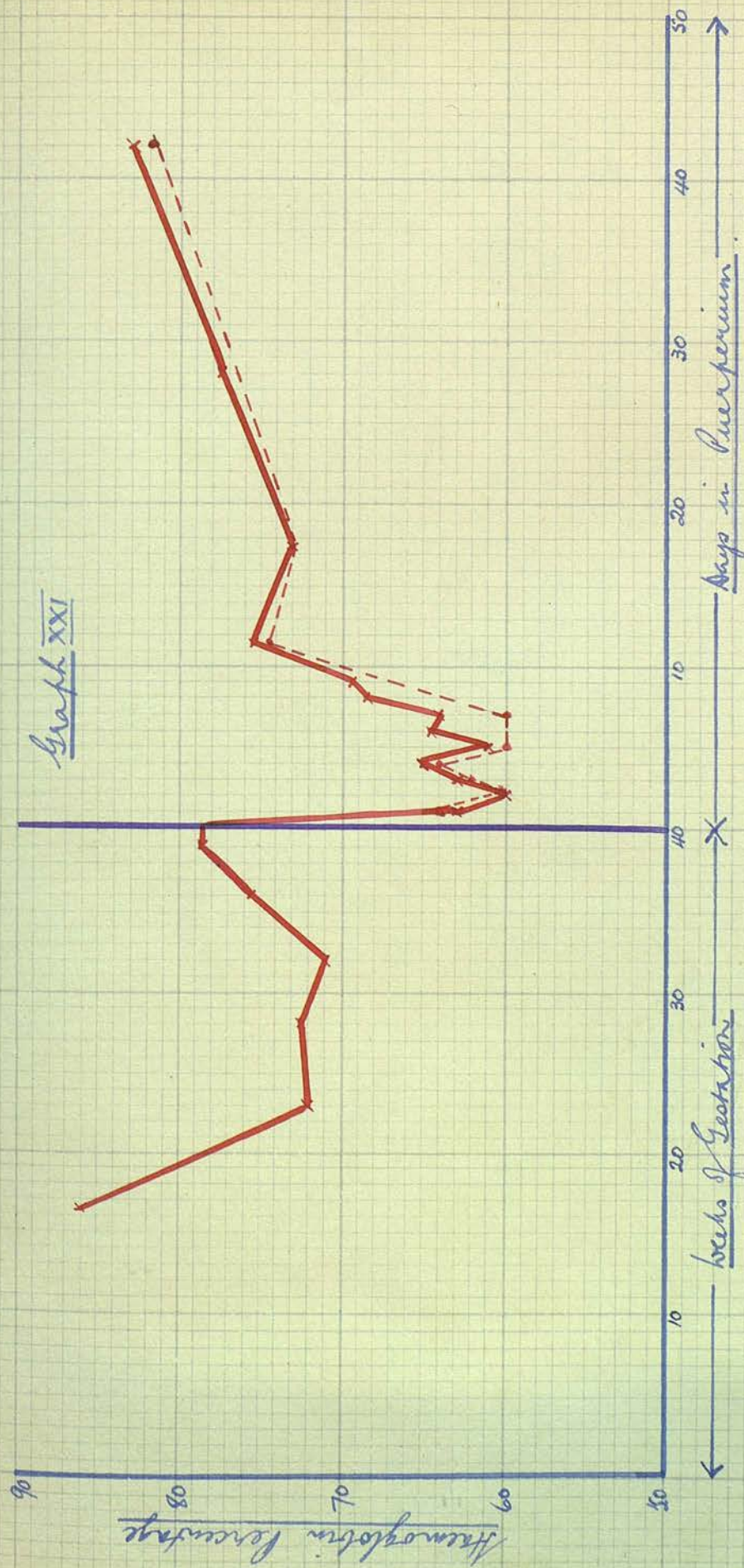
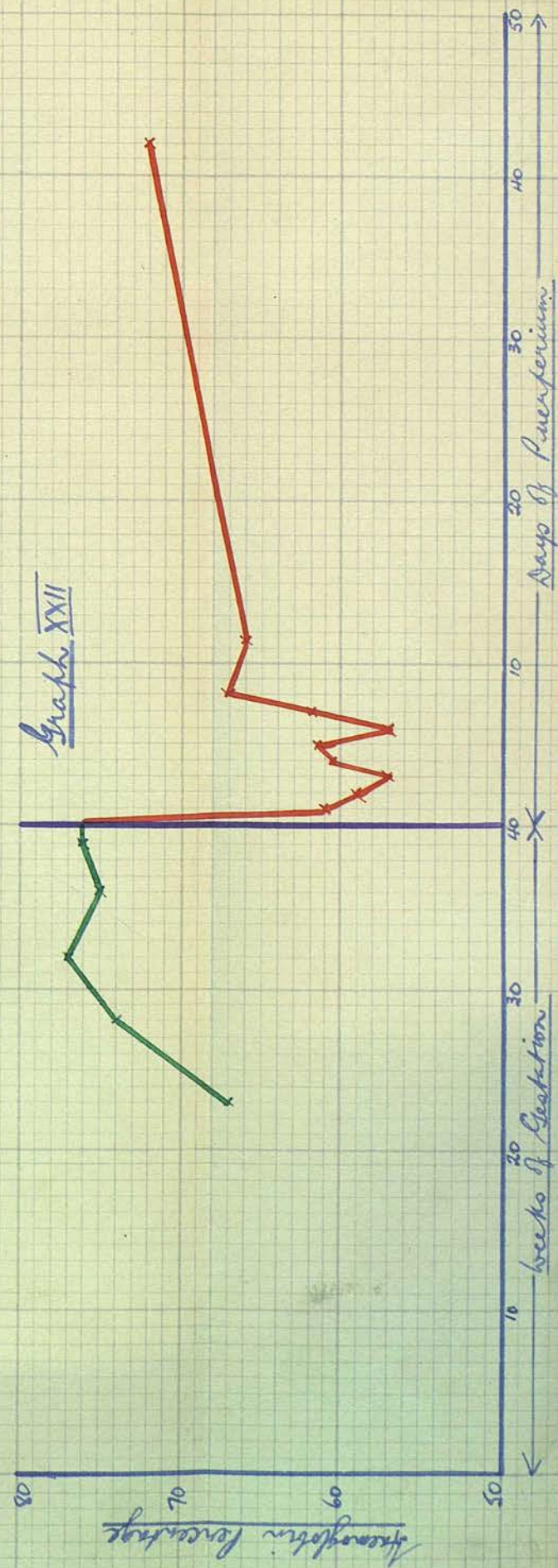
treated group had also an ante-natal anaemia and is excluded from this consideration. 5 out of the remaining six treated ante-natally also received iron in the puerperium and the results are shown in Graph XXI and Table XXIII. The 5 receiving no ante-natal iron were given iron after delivery, but only 3 were followed up to the end of six weeks after delivery. The remaining two returned to the care of other doctors at the end of a fortnight. The results of this group are shown in Graph XXII and Table XXIV.

See TABLES XXIII and XXIV.

The treated group reach full term with an average of 78.5% haemoglobin as against 76% in the untreated group. This is a difference of the same magnitude as was considered already in the normal groups. In the treated group here there is a maximal fall in haemoglobin after delivery of 18.5% while in the untreated group in pregnancy there is a maximal post-partum fall of 19%. The blood loss may therefore be considered to be equal in the two groups. At the end of six weeks however the group treated in pregnancy show an average of 83% (82% including the one not treated in the puerperium) as against 72% in the other group which was treated only in the puerperium.

We seem therefore to have here some confirmation of the suggestion that iron given in pregnancy when there is no anaemia may be stored and readily available/



Graph XXIGraph XXII



Weeks of Gestation	13-19	20-26	27-30	31-34	35-38	39-40
No. of Results	1	7	6	8	15	12
Range of Hgb. %	86	58-83	60-82	58-80	60-85	65-93
Av. Hgb. %	86	72	72.5	71	75.5	78.5

Days of Puerperium.	1	2	3	4	5	6	7	8	9	10-14	15-21	22-35	36-50
No. of Results	6	7	4	5	2	5	3	2	2	9	3	6	3
Range of Hgb. %	58-70	50-74	57-68	56-79	55-67	55-80	70-82	64-73	69-70	55-88	60-82	70-82	80-85
Av. Hgb. %	63	60	63	65	61	64.5	64	68.5	69.5	75.5	73	77.5	83

Number of Cases from which results were obtained = 6.

TABLE XXIII.

Weeks of Gestation	13 - 9	20 - 26	27 - 30	31 - 34	35 - 38	39 - 40
No. of Results		1	1	4	4	8
Range Hgb. %		67	74	67-87	70-79	60-84
AV. Hgb. %		67	74	77	75	76

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Days of Puerperium	1	2	3	4	5	6	7	8	9	10-14	15-21	22-35	36-50
No. of Results	3	5	4	2	2	3	1	5		8			3
Range Hgb. %	57-67	55-65	50-68	54-67	56-67	55-58	62	60-72		62-75			60-79
AV. Hgb. %	61	59	57	60.5	61.5	57	62	67		66			72

Number of Cases from which results were obtained = 5.

TABLE XXIV.



available for use should any iron shortage become manifest in the puerperium. Iron given when the need has manifested itself, as in the second group here, does not seem to be so readily or quickly used by the body for restoring the haemoglobin level. Perhaps we have here a hint of the delay that occurs in utilising the extra iron which is present in circulation at the time of delivery. There is no real iron lack and our investigation of normal cases fails to show any benefit to be derived in the puerperium by the administration of iron during pregnancy. The delay in the return of the haemoglobin to normal non-pregnant levels in normal non-anaemic women is a physiological process unaffected by the giving of extra iron. From the results of the other authors who reported benefit from iron, we must conclude that there was manifest in their cases some cause of iron shortage, perhaps excessive post-partum blood loss which however, could not be termed a true post-partum haemorrhage. There is therefore a definite indication that the immediate post-partum period should be controlled by blood haemoglobin estimations, as this, along with careful clinical observation, will enable us to decide which cases have suffered a more than normal blood loss. These cases will all require iron which will enable a speedier recovery to normal to be made, than if they were left untreated. Although we have shown that those receiving iron in normal pregnancy make a speedier recovery/

recovery after a severe puerperal blood loss, than those who have been equally normal in pregnancy but not treated with iron, we do not think that this is sufficient justification for adopting iron routine in pregnancy since the numbers involved are small and that minority can be treated effectively after delivery with ultimate restoration to normality.

Summary. The role of iron in the puerperium may be summarised by saying, that in a normal puerperium, with no excessive blood loss at parturition, the administration of iron, in either pregnancy, the puerperium or both, has no effect upon the haemoglobin since there is no iron shortage. Where such a shortage exists as in anaemia an excessive blood loss at parturition, the giving of iron has a beneficial effect. The delay in the restoration of a normal blood haemoglobin in the puerperium is physiological, probably due to the time lag in the break down of the extra haemoglobin in circulation at the time of delivery and its transfer into new red blood cells for circulation.

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IRON THERAPY AND THE ABNORMALITIES OF PREGNANCY  
AND THE PUERPERIUM.

So far the effects of administering iron have been considered in normal and anaemic patients in pregnancy and the puerperium. When we were considering the incidence of anaemia in pregnancy Table VII was presented which showed the other abnormalities which were met in the series of 104 cases. These other abnormalities can be divided again into treated and untreated groups in pregnancy and it will be on this basis that these groups will now be considered. The abnormalities considered have been selected as being those most likely to have an effect upon the blood picture and therefore most likely to be influenced or prevented by iron therapy. Other abnormalities there certainly were amongst the cases, mostly intra-partum such as the various forms of dystocia, but these were not considered to have any relation to the blood picture or iron therapy and have not been enumerated. The Table VII is given again here to facilitate reference to it from the text.

See TABLE VII.

The total number of cases in the series is 104, of which 50 received iron in pregnancy and 54 received no treatment. The above table will now be expressed in/



"Anaemia of Pregnancy"	A.P. Sepsis (Pyelitis)	P.P. Sepsis	Toxaemia	P.P.	Secondary Anaemia	
					A.P.	P.P.
"Anaemia of Pregnancy" 8						
A.P. Sepsis (Pyelitis)	5	1*		1*	1*	
Pyelitis		2				
Breasts		5		1*	2*	
Pelvic			3	1*	2*	
Hyperemesis			1	1		1
Albuminuria		1	5	1*		1*
P.P. Haemorrhage	3**			12		9**
Totals	11	5	3	1	5	16
Percentages	10.57	4.80	2.88	0.96	4.90	15.37

\* means the same patient is concerned in each horizontal group.

TABLE VII.

in different form giving the number in each category which received iron and which served as a control and expressing these figures as a percentage of the group to which they belong. There were 26 normal iron treated in pregnancy and 37 controls making up the total of 104 along with the abnormal cases. However, certain of the groups in Table VII were not altogether exclusive as will be noticed, therefore the same patient may be included in say Post-partum sepsis and Post-partum anaemia. The totals of the percentages will therefore be found to exceed 100% when the normals are included.

See TABLE XXV.

The "anaemia of pregnancy" group has already been considered and will not be further discussed here.

There were 5 patients who showed urinary infection in the form of pyelitis in pregnancy. In four of these the attack was acute and cleared up during pregnancy. However one recurred in the puerperium and is referred to again. One case might more accurately be described as a chronic B. Coli urinary infection which did not clear up until the termination of pregnancy. It was this latter case which manifested the hypochromic anaemia in pregnancy, which has been called a secondary anaemia since it is not strictly speaking like the anaemic group with no other complication. Four of the "pyelitis" group received iron in pregnancy/

	Iron		Control	
	Number	Percentage	Number	Percentage.
"Anaemia of Pregnancy"	5	10	6	11.10
A.P. Sepsis (Pyelitis)	4	8	1	1.85
Hyperemesis	1	2	-	
Albuminuria	2	4	3	5.50
Ante-Partum	1	2	-	
Post-Partum	8	16	8	14.80
Pyelitis	2	4	1	1.85
Breasts	3	6	3	5.50
Pelvic	3	6	-	
P.P. Haemorrhage	9	18	7	12.90
Totals	38	76	29	53.5

TABLE XXV.



pregnancy and one did not. This untreated patient was given iron in the puerperium. With the exception of the chronic case there was no instance of anaemia in the group and all returned to a normal average figure for the haemoglobin at the end of six weeks with this one exception.

In the toxaemic group we have only one case of toxic hyperemesis. This patient was so seriously ill in the early months that the advisability of terminating the pregnancy was seriously considered. Nevertheless by the fourth month she had completely lost her sickness and with iron therapy the blood reached normal standards in the later months. Labour was complicated and prolonged and a monster was born at full term. There was a brisk haemorrhage after delivery and a severe degree of secondary anaemia in the puerperium which was responding well to iron at the end of six weeks.

There were five cases who showed the usual signs of albuminuria with oedema and raised blood pressure in the later months. Two of these were given iron from the start of their ante-natal supervision and at no time in pregnancy or after showed any anaemia. Two of the three not given iron in pregnancy made as favourable a response as the two treated. The third untreated case in pregnancy was only seen a few days before labour and was found to have a hypochromic anaemia/

anaemia. Her puerperium was complicated by a severe post-partum haemorrhage leading to a secondary anaemia and subsequently a breast abscess. She made a slow but eventually complete recovery in little over six weeks on iron therapy. All five cases went to full term or labour was induced at the calculated date of delivery. One cannot therefore draw any conclusions from these few cases as to the role of iron in prevention of toxaeemias. Only one showed an anaemia in pregnancy which may have had other causes which we were unable to observe as she was only seen near term. Toxaemia therefore does not appear to have any effect on the blood picture as would be the case with Chronic Nephritis.

The single case of secondary anaemia in pregnancy has been mentioned as due to chronic bacterial infection of the urinary tract. Other types of sepsis which might give rise to symptoms were notably absent from the series and it is therefore impossible to state any conclusions regarding the role of infection in producing anaemia. However, it is interesting that the cases with an acute attack of pyelitis which cleared up, showed no anaemia or a favourable response to iron therapy, while the one with a chronic infection showed anaemia and a failure to respond effectively to iron during pregnancy.

Secondary anaemia in the puerperium was fairly frequent, there being 16 cases in all. Nine of those had/

groups (1) Pyelitis (2) Mastitis (3) Parametritis. There were three cases of pyelitis in the puerperium, one of which has been discussed as showing an acute urinary infection in pregnancy. The other two are indistinguishable except that one had received iron therapy in pregnancy and the other had not. Both were otherwise uncomplicated and made a good recovery after the acute attack. There were six cases with mastitis and only one subsided without pus formation. This one showed a post-partum anaemia and was untreated with iron in pregnancy. A second untreated in pregnancy was the case complicated by albuminuria and post-partum haemorrhage. The third untreated in pregnancy had a severe blood loss at labour and developed also a secondary anaemia. The three treated cases in pregnancy showed no other complication apart from the mastitis and it is therefore not surprising that these show a more favourable response in the haemoglobin level in the puerperium. Again no special advantage can be claimed for the iron-treated before delivery. There were three cases of parametric infection all following a complicated labour. They had all received iron during pregnancy. One developed a secondary anaemia which might have been due to a severe blood loss at labour. A second showed a reduced haemoglobin for a day or two after the infection while the third showed no other complications apart from the parametritis which was mild. All had normal haemoglobin levels/



levels at the end of six weeks following delivery.

The remaining abnormal group is the largest of the abnormal groups and has been referred to previously when considering the effects of iron therapy in the presence of an iron lack in the puerperium. This group of 16 cases presenting excessive blood loss at labour is largely made up of 12 cases presenting this as their chief feature. The three in this group with ante-natal anaemia have been considered before. The remaining four are derived from the groups enumerated in Table VII. There is therefore nothing to indicate that any complication of pregnancy is especially liable to be the forerunner of a severe or excessive blood loss at parturition. The group divides itself into nine treated and 7 untreated during pregnancy, so here again there is no conclusion to be drawn. That this group is the most frequent source of secondary anaemia in the puerperium is not to be wondered at. Only three in the group of 12 did not develop post-partum anaemia and these were all iron treated before delivery. This bears out the result already reported, that the iron given in pregnancy may be readily available to supply any iron lack when and if such a need arises.

This short study of the abnormal groups has failed to show any advantage to the iron treated cases so far as lessened incidence of complications of pregnancy and the puerperium are concerned. Also the small/

small number showing anaemia in this series does not allow us to say that the anaemic cases are more prone to complications of pregnancy and the puerperium. There were eight who showed merely the anaemia and three who appear in the group with post-partum haemorrhage. However this group of three make up only a small part of the group with excessive blood loss at labour.

The question of complications in pregnancy, parturition and the puerperium has often been commented upon in the literature from the haematological aspect, and the influence of anaemia and iron therapy in the causation or prevention of these complications has been investigated. The roles of anaemia and iron therapy are somewhat interwoven and sometimes difficult to separate in the reports in the literature. A brief résumé of the relevant facts will now be given before reaching conclusions regarding the roles of anaemia and iron therapy in the causation and the prevention respectively of complications.

Anaemia in pregnancy may be expected to have the same effects, as anaemia in the non-pregnant states, upon the general well-being of the mother. However, many of the anaemias discovered in pregnancy are not sufficiently severe for the mother to trouble about her complaints, which she is only too ready to attribute to her "state" at the time. Unfortunately then many/

many of these milder anaemias go unnoticed and unlooked for, and it is with the possible detrimental effects of these anaemias that we are chiefly concerned. The obvious ones differ in no way from those seen in the non-pregnant state and their effects upon the general health and well-being of the patient are so marked that they are usually diagnosed and treated effectively. May we expect any untoward effects from the neglect of these milder anaemias in pregnancy which are all too easily overlooked without a routine haemoglobin estimation?

Toxaemia. Perhaps the most elusive complication in the otherwise healthy woman who becomes pregnant is the so-called toxaemia of pregnancy. In the search for possible aetiological causes the blood condition of the patient has not escaped notice. The toxaemia of pregnancy is manifested by signs mainly referable to the kidneys which, previously healthy, do not seem able to cope with the increased demands of late pregnancy. These cases properly treated result in a complete recovery of kidney function after the termination of the pregnancy. The chief signs noted are, albuminuria, raised blood pressure and oedema, but all need not be present in any one case. Plass and Bogert<sup>78</sup> (1924) found a reduction in the plasma proteins at all stages of pregnancy, labour and the early puerperium in toxaemic cases as compared with normal cases. This/



This is presumably due to an increased dilution of the plasma and therefore we might expect a greater lowering of the haemoglobin in toxæmic cases. This plasma dilution would also fit into the frequency with which oedema is found in these cases. Whether it is correct to deduce from this fact that the anaemia has any direct relationship to the onset of the toxæmia does not seem to be so clear from the literature. Davis and Walker<sup>23</sup> (1934) however, showed that the group which they treated with iron, and which showed an improvement over an untreated group as regards the blood picture, also showed a lowered incidence of raised blood pressure of the toxæmic type.

The results of Moore and Pillman-Williams<sup>69</sup> (1936) are in agreement with this. They found only one toxæmic case in thirty-five iron treated cases and six toxæmic cases in thirty-four untreated cases in pregnancy. The 6 toxæmic cases only began to show symptoms when the haemoglobin fell to 70-79%. This of course may only confirm the dilution of the blood found by Plass and Bogert and is no direct proof of the causal relationship of anaemia to toxæmia. In a group of 67 patients with albuminuria investigated by O'Sullivan<sup>76</sup> (1932), 21 had albuminuria of the toxæmic type while the remainder had albuminuria due to urinary infections. The incidence of anaemia was higher in the former group and 11 of these anaemic ones in this group were treated and seven showed a favourable/

favourable response to iron after three weeks treatment. These cases who responded also showed an improvement in the albuminuria. Whether the iron therapy was the sole cause seems doubtful as these cases are known from experience to respond to rest and proper diet. Further doubt is thrown on the causal association of anaemia and toxæmia by the observations of Boycott<sup>8</sup> (1936) who found no greater incidence of toxæmic cases in his anaemic and non-anaemic groups in pregnancy and of Reid and McIntosh<sup>81</sup> (1937) who concluded from a study of 1094 cases that there was no relation between toxæmia and anaemia.

The conclusion must be that anaemia has not been shown to be an aetiological factor in the production of toxæmia. Rather is it more likely to be the opposite, that toxæmia tends to produce anaemia, since it is well known that nephritis leads to a secondary anaemia. In 300 pregnancies Moore<sup>68</sup> (1930) found that the lowest haemoglobins were found in those with a complicating chronic nephritis. Also Stieglitz<sup>86</sup> (1931) found that anaemia was commonly associated with nephritis in pregnancy and that the former had an adverse effect upon the latter both during pregnancy and in regard to the prognosis of the nephritis. The fact that albuminuria in pregnancy improves with improvement in the anaemia (O'Sullivan<sup>76</sup> (1932)) may be an example of symptomatic improvement without any relation/

relation to the true cause and therefore not a proof of the aetiological role of anaemia in toxæmia of pregnancy.

Labour. Only two authors comment upon any connection between anaemia in pregnancy and its effect upon labour and these two disagree. Davis and Walker<sup>23</sup> (1934) found a shorter labour in their iron treated cases who had shown a response to treatment while Reid and McIntosh<sup>81</sup> (1937) could find no relationship between anaemia and any abnormality in labour. Regarding blood loss at labour, Boycott<sup>8</sup> (1936) adds his confirmation that the anaemic group lost no more than the non-anaemic. There seems therefore to be no co-relation between anaemia and progress of labour. It can be well believed however, that the results of a post-partum hæmorrhage to the mother may greatly depend upon whether she is anaemic or not before the onset of labour.

Maternal Mortality. No authoritative statement on this fact can be found. Lull<sup>54</sup> (1937) in his discussion of pregnancy anaemia gave it as his opinion that the reduction of anaemia would be a definite factor in reducing maternal mortality, but no facts or figures are given in support of this statement.

Maternal Morbidity. A lower maternal morbidity for those treated with iron in pregnancy was claimed by Davis and Walker<sup>23</sup> (1934) and Labate<sup>49</sup> (1939).

The/



The latter showed an incidence of 14.8% morbidity in 325 iron treated cases as against an incidence of 19.5% in 556 untreated cases. Other morbid conditions ranging from dental caries to more serious conditions like tuberculosis and post-partum psychosis have been claimed to be influenced by the anaemic state in pregnancy (Lull<sup>54</sup> (1937)). The same author also believed that anaemia led to delayed rate of involution of the uterus after delivery.

Puerperal Septicaemia was not found by Reid and McIntosh<sup>81</sup> (1937) in their cases, but they thought that anaemia might result in a greater incidence of Puerperal Pyrexia from various causes.

Breast Feeding. Regarding the ability to breast feed Reid and McIntosh<sup>81</sup> (1937) found no correlation between this and the anaemic state in the mother but Lull believed that this function too would be adversely affected by anaemia.

In regard to the mother then it may be said that anaemia exposes her to much the same complications as one would expect to find in the non-pregnant state, only during pregnancy and especially the puerperium the opportunities for infections occurring are increased. Her resistance is lowered to bacterial infection as a result of the anaemic state.

Birth Weight. This has been shown to be an important factor in regard to the total amount of iron contained in the foetal circulation (See later).

Reid/

Reid and McIntosh, however, have not found any correlation between the birth weight and maternal anaemia, so that the children of normal and anaemic women seem to stand an equal chance in regard to the iron store present at birth.

Miscarriage. Miscarriage and Prematurity are believed to be more frequent in anaemic women than in the non-anaemic (Whitby and Britton - "Disorders of the Blood" and Lull<sup>54</sup>(1937)).

Foetal Mortality. Death of the foetus was shown to be more common in the untreated cases of Davis and Walker<sup>23</sup>(1934) and Stillbirth was more frequent in first pregnancies when the mother was anaemic (Reid and McIntosh<sup>81</sup>(1937)) but not in subsequent pregnancies even if the mother was anaemic.

Neo-natal deaths and infant mortality were found to be increased as a result of maternal anaemia (Reid and McIntosh<sup>81</sup>) but most of these cases were of low social status.

Conclusions. It may be stated that from this survey of the literature and our own abnormal groups, anaemia in pregnancy has not been shown to bear any direct relationship to the more serious complications of pregnancy, parturition or the puerperium. The ability of the mother to withstand bacterial infection is lowered by anaemia and such complications may be expected more frequently in the anaemic in pregnancy, but/

but more especially in the puerperium when the chances of infection are increased. However, the ability of infection to produce anaemia has also to be remembered in each case.

To the offspring the effects of maternal anaemia seem to be to increase the risks of earlier life, but here there are probably other factors at work of equal importance with the maternal anaemia.

Regarding the advantages of iron therapy in pregnancy, it may be said that the treated groups show no advantage over the untreated in respect of the incidence of complications before, at or after labour, but that iron has a decided beneficial effect upon the hypochromic anaemic of pregnancy. In the improvement of the blood condition in anaemic women, iron leads to the increased well-being of the mother.

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## THE ANAEMIA OF PREGNANCY.

The main purpose of any investigation such as this present is to enable one to arrive at some estimate of the seriousness and frequency of anaemia in pregnancy with a view to treating and alleviating such anaemia when it is found. Up to this point we have considered normal levels of haemoglobin in pregnancy and the normal behaviour of the blood during the forty weeks of gestation and the first six weeks after delivery. This has led us to consider the rôle of iron in affecting the blood picture in normal and abnormal cases, but beyond stating that the anaemic cases found all belonged to the hypochromic type and studying briefly the effects of this anaemia on mother and child, we have not fully discussed the problem of anaemia in pregnancy. It is intended to do so now, but prior to this we shall consider the Iron Metabolism of the Mother and Foetus, since this is of prime importance in any discussion upon Anaemia in Pregnancy, which in this series is completely and in this country almost completely, of the hypochromic, iron-deficient type.

The Maternal Iron Metabolism. In pregnancy the fundamental iron metabolism differs not at all from that of the non-pregnant and therefore the remarks will largely apply to the non-pregnant as well as the pregnant. However, after the consideration of the main facts/

facts we shall indicate any special points referable to the pregnant state alone.

Iron is an essential element of the body and although so absolutely necessary, it only occurs in small amounts in the body. The figure quoted by Wright in "Applied Physiology" is 4-6 Gms. About 3 Gms. of this is found in the red cells while the remainder is found in the chromatin of the nuclei and in the cytoplasm of the tissue cells. Heath and Patek<sup>42</sup> (1937) state that Iron is present in three forms in the human body:- (1) 2.67 Gms. in the circulating haemoglobin of a person with 15.6 Gms. per 100 ccs. (2) Depots of latent iron chiefly in the liver, spleen, lymph nodes, kidney and marrow. (3) Iron derived from broken down red cells. The total they believe to be about 4.3 Gms. Hahn<sup>40</sup> (1937) prefers to talk of the iron as being present in (1) Haemoglobin (a) In Circulation (b) In Muscle. (2) Parenchyma. (3) Liver etc. as storage iron.

It will be seen later that the child starts life with a store of iron but ever after is dependent upon an external supply of this element which has to be ingested. Normally this has to be obtained from the food eaten, but in states of anaemia due to lack of iron the loss is made good more effectively by the ingestion of inorganic iron.

The study of the ingestion of inorganic iron has made/

made it possible for us to understand something of the way in which the body deals with iron. Hahn et al<sup>41</sup> (1939) studied the course of iron transport, storage and excretion by means of the ingestion of radio-active iron. It is found that absorption occurs in the duodenum and upper jejunum. The amount absorbed depends largely upon the physiological state of the animal as was shown in dogs. An anaemic dog (Hgb. = 39%) given 220 mgms. of radio-active iron over four days absorbed 9.3 mgms. A normal dog given 650 mgms. over the same period only absorbed 0.24 mgms. It will be seen from this observation that the amount of iron required in health is small. This is due to the fact that very little is excreted and the iron derived from the catabolic processes is retained within the body for further use. The large bowel excreted a very little iron, and a trace - perhaps 1 or 2 mgms. - is excreted in the urine in the 24 hours (Starling's Physiology). Wright in the latest edition of his book does not seem to doubt that this experiment in the dog is applicable to the normal and anaemic human subject also. However, doubt has been thrown upon this subject as is exemplified by two recent American experiments which are flatly contradictory in regard to the results obtained by giving iron to normal humans. Moore, Roberts and Minnich<sup>99</sup> (1941) report absorption while Ross and Chapin<sup>100</sup> (1941) report only minimal/



minimal absorption as in the case of the normal dog. Some experiments reported earlier by Widdowson & McCance<sup>97</sup> (1936), Sankaran & Rajagopal<sup>98</sup> (1938) and Widdowson<sup>93</sup> (1939) would indicate absorption of iron by the normal human, but that this is a super-normal absorption, not met with except experimentally and not giving rise to any premanent increase in the haemoglobin level, was shown recently by Fowler and Barer<sup>101</sup> (1941). These experiments however, are all in agreement with the theory of controlled absorption, rather than controlled excretion by the bowel, as propounded by McCance and Widdowson<sup>59</sup> (1937). These authors were dissatisfied with the view of the large bowel as a true excretory organ since it was difficult to be sure how much iron was absorbed and excreted and how much merely passed through the bowel. The absorption of iron from bowel to plasma depends upon a relatively higher concentration existing in the bowel lumen than in the plasma. Normally the latter level is kept low because the storage organs remove any excess immediately it occurs in the plasma. In the abnormal experimental conditions reported it appears that the great increase in iron in the bowel lumen tends to a rise in plasma iron above physiological levels thus stimulating extra haemoglobin formation. However after a time the body adjusts itself to this altered state (Fowler and Barer<sup>101</sup> (1941)) and restores a normal/

normal haemoglobin level. This might be assumed to occur by the storage organs gradually adapting themselves to the storage of excess iron thus reducing the raised plasma iron to normal and preventing further new haemoglobin formation. That the absorption of iron is controlled is not doubted by Ross and Chapin<sup>100</sup> (1941), who did not find any difference between the normal human and the normal experimental dog in regard to iron absorption. However, they thought that the tissue iron in the gut mucosa was the factor determining the absorption of iron from the bowel lumen.

Returning to the experiment on Iron absorption it was noted that the dog only absorbed the small quantity of 0.24 mgms. in 4 days. This raises the question of the human needs in normal health and the amount absorbed from the food stuffs.

In recent papers Drummond<sup>27</sup> (1940) and McCarrison<sup>60</sup> (1940) give 15 mgms per day as the human requirement. However, it is known that many maintain iron equilibrium on smaller amounts than this (Davidson and Fullerton<sup>19</sup> (1938)) and Wright states that the ordinary dietary only contains 5-10 mgms and that smaller amounts than this may suffice.

The question of the availability and the absorption of iron is therefore raised. The actual amount absorbed need only be very small as is shown by Davidson and Fullerton<sup>19</sup> (1938) who studied the iron loss and intake/

intake in women of child-bearing age in Aberdeen.

In the non-pregnant woman who is not losing an excessive amount at menstruation, this latter loss is compensated for by daily absorption of 2.5 mgms.

The absorption of iron has attracted considerable attention, particularly in regard to its relation to gastric activity. In the pregnant state where gastric function is so often subnormal, the possibility of this defect being responsible in part for the hypochromic anaemia of pregnancy has been investigated and the results are pertinent to the present consideration of the normal female. Mettler and Minot<sup>65,66</sup>

(1929 & 1931) reported in all 10 cases of secondary anaemia associated with defective diets and gastrointestinal upset or chronic blood loss. These cases were fed by tube with a beef-steak medium rendered either acid or alkaline as desired. The results were gauged by the reticulocyte response. The medium itself was without effect on the blood response. Small doses of iron were more effective in an acid than in a neutral or an alkaline medium. Larger doses were effective regardless of the reaction of the medium but acidity was found to be an added advantage.

Mettler et al<sup>57</sup> (1933) in a further study of chronic idiopathic hypochromic anaemia investigated 10 patients all of whom with one exception had no gastric hydrochloric acid after alcohol test-meal. The one exception/



exception had only a trace of hydrochloric acid. Large doses of iron (6 Gms. of Iron and Ammonium Citrate) were administered to some of the patients, with good results. A diet rich in iron was given to three cases for 60 days but the treatment failed to improve the blood picture. These three rapidly responded to treatment as in the first group. In order to ascertain the role of the gastric secretion, four patients were given a meal pre-digested with normal gastric juice over a period of 20-42 days. The response was similar to that of those taking iron. The authors conclude that there is a failure to utilise organic iron in an alkaline medium.

Beebe and Wintrobe<sup>4</sup>(1933), studying 5 patients with the same type of anaemia, virtually carried out the same experiment. Their patients, however, when given a pre-digested meal failed to show any blood response. The addition of a small dose of iron resulted in improvement, but the best result was obtained by giving 6 Gms. of Iron and Ammonium Citrate alone each day. They are unable to draw conclusions regarding the influence of normal gastric secretion on iron absorption.

Kellog and Mettler<sup>46</sup>(1936) took the opportunity to study the iron absorption in 4 anaemic male patients. The anaemia was the result of haemorrhage from a peptic ulcer. It was known that inorganic iron is effective in these cases. The patients while on alkalis/

alkalis and a Sippy regime showed no regeneration of haemoglobin. A diet rich in iron (12-15 mgms. per diem) was then given and the alkalis continued. There was still no rise in haemoglobin but a definite regeneration of red blood corpuscles, showing an absorption of stroma-building material. The alkalis were then stopped and the same diet rich in iron produced a rise in haemoglobin corresponding with the response to inorganic iron.

From these investigations it seems clear that organic iron cannot be utilised in the absence of hydrochloric acid. It is also known that inorganic iron can be effective even in an alkaline medium and is more effective in large doses. One discrepancy arises in these reports, namely the totally different results obtained by Mettler et al and by Beebe and Wintrobe in feeding a pre-digested meal to an anaemic patient. In the former authors' report there was a good response, and in the latter authors' report no response. Davidson and Fullerton<sup>19</sup> (1938) believe the chief role of hydrochloric acid to be the liberation of iron from the food in a suitable form for absorption. They admit that the hydrochloric acid probably plays a minor role in absorption. As they point out, there are no figures known which give the availability and the absorption of iron in cases of achlorhydria. The only explanation of the discrepancy in the results mentioned/

mentioned would appear to be on the grounds of availability. The diets which were pre-digested were not identical and apparently the iron has been more easily made available from the iron rich diet than from the beef-steak diet which was used without response by Beebe and Wintrope.

Thus far, therefore, we know that in health the organic iron in the diet has to be made available for absorption by the action of hydrochloric acid and that the acid may be further responsible for the absorption of the available iron. Only small amounts appear to be required daily and it seems clear that the optimal dietary needs in regard to iron as quoted by Drummond and McCarrison are generous estimates.

The iron of the diet is believed to be absorbed in the form of the ferrous chloride and its absorption as already seen occurs in the duodenum and upper jejunum.

Continuing the study of absorption of radioactive iron it was seen that the iron was absorbed into the portal blood plasma. Absorption, as far as is possible, takes place within 18 hours of a single dose being administered. The iron is thence carried to the liver and bone-marrow.

Iron is an essential constituent of haemoglobin, which acts as the oxygen carrier from lungs to tissues, and is therefore of prime importance. It also has a part to play in the oxidative processes in the tissues (Heath/



(Heath and Patek<sup>42</sup>(1937)). Haemoglobin is a complex organic substance made up of two main parts; the protein part (globin) and the iron containing part (haematin) which is an organic iron compound. Iron is used by the body in the formation of haematin and the presence of copper acting as a catalyst is probably required for this process. The absorbed iron therefore is transferred to the red blood cells in the bone marrow and the absence of sufficient iron leads to cells imperfectly filled with haemoglobin i.e. an hypochromic anaemia.

In the experiment using radio-active iron it was shown that iron reaches the red blood cells within a few hours of ingestion. This shows the speed with which the iron can be transferred from plasma to cell by the bone marrow.

The red blood cell having fulfilled its function of oxygen-carrier, in virtue of its haemoglobin content, eventually is destroyed, probably after such a short period as three weeks. (Starling). The haemoglobin is then broken up into its two main parts - globin and haematin - the latter is further broken up into an iron-free fraction called bilirubin and iron which is stored in the reticulo-endothelial system in liver, spleen and bone marrow or used again for further haemoglobin formation (Heath and Patek<sup>42</sup>(1937)).

It seems from this that the iron cycle within the body could go on without absorption of iron from without/

without, except in so far as loss of iron by haemorrhage would require to be made good. Although such a state of affairs nearly exists there is a small wastage of iron due to excretion in small amounts by the large bowel and by excretion of a trace in the urine. The experiment on absorption of iron in dogs already quoted bears out the fact that animals in iron equilibrium absorb very little iron even when large amounts are fed. From this we deduce that only small amounts are required to make good the wastage by bowel and kidney. The excess ingested passes through the intestine.

In the adult female there is in addition the Physiological wastage due to menstruation but this, as was shown by Davidson and Fullerton (1938), can be made good by the daily absorption of 2.5 mgms.

It will be seen therefore that the human body is extremely economical in its use of iron. Only a small amount is absorbed from the diet in health. Iron can be used over and over again in the formation of haemoglobin and only small amounts are excreted by the kidney and bowel.

Turning now more particularly to the consideration of the pregnant state and its special needs, namely the provision of the foetus with adequate iron for blood formation and storage and the maintenance of the mother's haemoglobin at a level greater than in the non-pregnant state, there are one or two physiological/

physiological facts requiring consideration.

In the study of foetal iron metabolism we shall see how much iron is obtained by the foetus from the mother but here it may be stated that this probably does not greatly exceed that which would normally have been lost by menstruation over a period of 40 weeks. The total increase in circulating haemoglobin will require an increased absorption of iron over the non-pregnant state if the body stores are not to be depleted by pregnancy.

It will be seen therefore that the total increase in the iron required in pregnancy cannot be much greater than that required in the non-pregnant state.

Coons<sup>16</sup> (1932) investigated the iron retention in pregnancy in 9 women in whom intake and output of iron was carried out at different stages of pregnancy. The output in urine was found to be small. Storage was found to be considerable especially in the early months but falling off in the later months when the foetal demand became greatest. In the first six months storage and retention exceeded foetal demands but in the last three months the demand exceeded the amount retained. The estimate given of the iron requirements for the whole of pregnancy is a daily absorption of 3.2 mgms. This figure would appear to be in correspondence with the figure of 2.5 mgms. given by Davidson and Fullerton for the non-pregnant.

Although/



Although the demand for iron is not increased greatly yet there are other factors in pregnancy which may be considered almost physiological and which tend to lead to a lowered intake and absorption of iron. The first of these is the gastro-intestinal upset so common in pregnancy which very often results in the ingestion of a diet not adequate in food-stuffs containing iron. Secondly an achlorhydria or hypochlorhydria is a frequent accompaniment of pregnancy and already we have seen how achlorhydria may impair absorption of organic iron. These factors taken together - the slightly greater iron need and the factors tending to limit absorption - show the need for a raised intake of iron in the dietary. The figure quoted by Drummond and McCarrison is 20 mgms. per diem in the diet. This should certainly insure an adequate absorption in the absence of pathological conditions.

Apart from the increased maternal need to supply iron to her offspring and the above possible alterations in the physiology of absorption there are no other features of iron metabolism in the pregnant female which have not already been discussed for the normal non-pregnant woman.

The Foetal Iron Metabolism. It is immediately obvious that any iron content possessed by the foetus must/

must of necessity be derived from the mother. The probable source of this iron is the circulating haemoglobin, the iron of which is transferred to the foetus for the manufacture of the foetal haemoglobin, for storage in the liver and the iron found in the tissues.

As early as 1889 Bunge<sup>9</sup> focussed attention on the storage aspect of iron by the foetus when he drew attention to the fact that in dogs the mineral content of maternal milk was identical with the mineral content in the body of the young dog, except in respect of iron, which was only one sixth as concentrated in the milk. This implied a probable shortage of iron in the milk feeding period and the possibility of some provision having been made by nature to counteract this factor tending to produce anaemia. The same thing was later demonstrated by Abderhalden<sup>1</sup> in 1898 in the case of rabbits. Bunge<sup>10</sup> in 1892 following up his first experiment showed that the iron content of young mammals is highest at birth, but diminishes during the milk feeding period. Also weight for weight the liver of the foetus contains five times as much iron as the adult liver. That there is a drain of iron from mother to foetus is undeniable and Hugonnet<sup>43</sup> (1899) at this early date showed that two-thirds of the iron present in the body of the foetus at term, is laid down in the last month.

The/

The function of iron in the foetal haemoglobin is the same as in the mother namely oxygen carriage, from placenta to tissues. Storage of iron must obviously be concerned with tiding over the milk-feeding period when the iron supply is limited.

Numerous observers have been interested in the foetal iron metabolism and particularly in the fact that the foetus is almost never born with a depletion of red blood corpuscles and haemoglobin. The only references to anaemia in the new-born, which one can find, are given by Greenthal<sup>39</sup> (1930) who quotes six previously reported cases and adds one of his own, in which he adopts the explanation that there has been some temporary upset of the blood forming organs. All other observers (Rowlands<sup>83</sup> (1924); Allan<sup>3</sup> (1928); Castle and Strauss<sup>14</sup> (1933); Strauss<sup>87</sup> (1933) & <sup>88</sup> (1934); Mackay<sup>63</sup> (1935); Davidson et al<sup>18</sup> (1935); Irving<sup>44</sup> (1935); Streat and Gottlieb<sup>37</sup> (1936) and <sup>38</sup> (1939); Smallwood<sup>84</sup> (1930)) have reported a normal complement of red blood cells and haemoglobin in all the children examined by them at or shortly after birth.

Although this point appears to need no confirmation the foetal haemoglobin, at birth or within 24 hours of birth, was estimated in 67 of the children born to the 104 cases reported in this series. The blood was obtained either from the cord or from the heel of the child. 41 of these were derived from the normal/



normal groups and the remainder variously from the abnormal groups reported. It was not possible to draw any distinction between the children of anaemic mothers and those of normal mothers, so far as the haemoglobin level at birth was concerned. There were no children anaemic at birth and the average for the whole group was 122.5%. This figure, as was pointed out earlier, is not strictly comparable as a percentage with the figures given in the case of the mothers' haemoglobin, since there was the longer time required for conversion of the foetal haemoglobin to acid haematin. However, it does show that the foetus starts life with a very high haemoglobin content in the blood and that no infants in this series are anaemic.

No worker in the list mentioned above, with the exception of Smallwood, found any advantage in the blood at birth in the children of mothers who received iron in pregnancy as compared to the children of a control group of mothers or even anaemic mothers in Pregnancy. However this may be - and all the evidence points to no initial advantage for either group - it has been clearly demonstrated by numerous authors that Nutritional Hypochromic Anaemia occurs in many children towards the end of the milk feeding period, so that some explanation must be sought.

That the maternal milk is a poor supply of iron was shown very early (Bunge<sup>9</sup> (1889)) and it is known that/

that Cow's milk is a still poorer supply for human infants. This is one factor which has been investigated and found to have some effect upon the production of the anaemia. This, however, is not strictly concerned with the foetal metabolism of iron and will not be further considered. The question of foetal stores of iron throws much more light upon the foetal metabolism of iron. An obvious explanation perhaps of the development of anaemia in infancy would be the depletion of the iron reserves of the foetus and so it was thought that anaemic mothers might produce children with inadequate reserves. Some connection was therefore sought between the blood condition of the mother during pregnancy and the development of anaemia in the offspring. Plenty of evidence is forthcoming to support the contention that anaemia in the mother predisposes to anaemia in the offspring. Strauss<sup>87</sup> (1933) studied two groups of patients (1) Normal infants of mothers who were normal in all respects save their anaemia during pregnancy and (2) Normal infants of mothers who had no abnormalities in pregnancy. The first group of infants and mothers showed anaemia at the end of one year. The second group showed no anaemia. In a control group of anaemic pregnant women during the last three months of pregnancy, iron was given with good results to mother and child after one year post-partum. The results were taken to indicate a failure by the foetus to store sufficient iron during intra-uterine/

intra-uterine life.

Mackay<sup>63</sup> (1935) admits that her evidence is meagre but concludes from her studies that maternal anaemia has probably a part to play in the production of infantile anaemia. Irving<sup>44</sup> (1935) also lends support to this view while Gottlieb and Streat<sup>37 & 38</sup> (1936 and 1939) showed that the children of anaemic mothers while possessing at birth a greater polycythaemia and full complement of haemoglobin show a more rapid fall and a less favourable blood picture after four weeks, than the children of normal women. Smallwood<sup>84</sup> (1936) also lends support to these views. It appears that these views have been expressed sometimes without adequate control as in the cases quoted by Strauss where the numbers are small and since no note is made of birth weight, rate of growth and the possibility of inter-current infection - facts shown by Fullerton<sup>34</sup> (1937) to be of prime importance - these factors cannot be discounted as influencing the results.

The subject has been placed upon a quantitative basis by Fullerton<sup>33</sup> whose work has placed before us certain facts which are lacking in the other works mentioned and while carrying weight also help us to an understanding of the question of iron storage in the foetal liver. The total quantity of iron in the foetus at birth is taken on an average to be 450 mgms. About 80% of the iron is in circulation, as calculated from/



from the blood volume and the haemoglobin percentage at birth. This accounts for about 330 mgms. of the total and is present in the circulating blood. In the tissues there are 70 mgms. and in the liver 50 mgms. Assuming the child to have the normal amount of haemoglobin at 9 months (86% Haldane according to Mackay<sup>63</sup> (1935)) then it is shown that there will be 333 mgms. in circulation, while the tissues will contain 175 mgms. This gives a total of 508 mgms. exclusive of the liver reserves. If the original 50 mgms. in the liver are used up at 9 months, then only an additional 58 mgms. is required from the diet to give the normal figure of 86% for the haemoglobin. An infant on breast milk is more than likely to absorb this amount. Further if it is assumed that the foetal liver at birth contained no iron then the lack of this 50 mgms. would only result in a lowering of the haemoglobin to 73% at nine months. The lack of the 50 mgms. is therefore not an adequate explanation of the anaemia found in infants since this anaemia may be of much greater severity. In addition it seems highly improbable that the mother, even admitting her to be anaemic, should fail to supply 50 mgms. for liver storage out of the total of 450 mgms. required, because this small amount would hardly affect the maternal haemoglobin level at all (Fullerton<sup>33</sup> (1936)).

The author therefore seems justified in the conclusion that failure to store iron in the foetal liver/

liver is not a factor of significance in the production of the anaemia of infancy. His figures of cases quoted also show that the maternal haemoglobin level does not affect the foetal haemoglobin at the first and eighth days, which is in agreement with the previous authors quoted, and in a large series he has shown that the maternal haemoglobin level taken at the time of examining the infant is not in any way correlated with the haemoglobin level of the infant from 9-16 months of age. In another series of 113 cases the maternal haemoglobin was known during pregnancy but this bore no definite relationship to the haemoglobin level in the child between 9 and 16 months of age. True it is that infants of mothers with less than 70% haemoglobin in pregnancy gave an average haemoglobin of 64.5% which was 5-6 per cent lower than the groups of children from mothers with higher haemoglobin. However, the author does not think this amount of difference justifies any deductions being made. It certainly does not indicate any failure of liver storage by the foetus. Thus we learn that besides having a normal complement of red blood cells and haemoglobin at birth, every child may be assumed to possess adequate stores of iron in the liver.

The discrepancies which therefore arise between the authors quoted have to be explained on some other basis than that of iron storage and this is done by Fullerton/

Fullerton<sup>34</sup> (1937) who showed that the real factors leading to the anaemia were low birth weight - which means less circulating iron (cf. blood volume in relation to weight) which is the main iron content of the foetus - artificial feeding with its poor iron content and infections in infancy.

To summarise the topic of Foetal Iron metabolism it may be stated that the foetus obtains sufficient iron from the mother in order to start life with a normal blood picture. The iron in circulation is in the haemoglobin of the foetal blood. This haemoglobin is somewhat different to the adult haemoglobin and requires a longer time to be converted into acid haematin by hydrochloric acid (Whitby and Britton - "Disorders of the Blood"). The function of the foetal haemoglobin, however, is the same as in the adult - namely oxygen carriage - but the carriage of oxygen in the foetus is from placenta to tissues and not from lungs to tissues as occurs after birth.

We may also assume that there are adequate stores of iron in the foetal liver, which is particularly rich in iron as compared to the adult liver and that there is no shortage of iron in the tissues.

Throughout intra-uterine life the iron content of the foetus is constantly increasing and there appears to be no excretion. Any break-down of blood cells with liberation of iron doubtless leads to this iron being available for new red cell formation. The chief increase in the foetal iron content occurs in the last trimester of pregnancy.



Anaemia in Pregnancy. Anaemia in Pregnancy has been studied intensively over many years and now in the light of modern haematological knowledge it is possible to study these more exactly than was possible formerly. However, differences of opinion still exist and are evident to anyone perusing the relevant literature .

In a discussion of this subject it is useful to look at the classification of the anaemias of pregnancy given by Osler in 1919 and representing the views at that time. His classification is as follows:-

1. Anaemia in Pregnancy secondary to a post-partum haemorrhage.
2. Severe Anaemia of Pregnancy.
3. Severe Post-Partum Anaemia.
4. Acute Anaemia as a result of sepsis.

Alongside this let us consider the classification given in the latest edition of "Disorders of the Blood" by Whitby and Britton. This may be taken as a fair representation of the modern views upon the subject.

1. Hypochromic Anaemias.

- A. Idiopathic Hypochromic Anaemia complicated by Pregnancy.

- B. Hypochromic Anaemia induced by Pregnancy.

2. Macrocytic Anaemias.

- A. Macrocytic Anaemia complicated by Pregnancy.

- B. Macrocytic Anaemia induced by Pregnancy.

3./

3. Hypoplastic Anaemia.

4. Haemolytic Anaemias.

5. Secondary Anaemia complicated by Pregnancy

e.g. Streptococcal and Staphylococcal Septic-aemia, Malignant Disease, Lukaemia, Nephritis, Haemolytic Icterus, Hookworm Infection, Malaria, Syphilis etc.

The first group given by Osler is included in the Secondary group of Whitby and Britton and the onset of the anaemia is from an obvious cause. Similarly the fourth group of Osler falls into this same category as do groups 2, 3, and 5 of the classification given by Evans<sup>29</sup> (1937). The second group of Osler probably corresponds to group 2B. of the above classification and is mentioned by Rowlands<sup>83</sup> (1924) who described two cases of the pernicious or haemolytic anaemia of pregnancy occurring in the latter months of pregnancy and in the puerperium. These descriptions were written before the discovery of the cause and the cure of Pernicious Anaemia, but the accuracy of the description will be referred to again shortly. The third group given by Osler is believed by Whitby and Britton to correspond to their hypoplastic anaemia where a macrocytic anaemia of pregnancy has failed to respond to liver in the puerperium and where treatment has to be continued by Liver and Iron for a prolonged period after delivery/

delivery before the hypoplastic marrow is enabled to recover. The hypoplasia is believed to be due to the strain upon the marrow during pregnancy. In the days before liver therapy the seriousness of this post-partum anaemia can be understood. A big gap in the knowledge of the subject in 1919 and our knowledge to-day is therefore obvious.

The group which alone is commonly seen is the first group of the hypochromic anaemias, but before attempting to analyse our knowledge of this group a few remarks will be passed upon the other groups for the sake of completeness.

With the discovery by Minot and Murphy in 1926 of the role of liver in pernicious anaemia great interest has centred in this type of anaemia. A discussion is outwith the present intention, but the nature of the anaemia has been understood and in pregnancy a type similar to pernicious anaemia has been described. Allan<sup>3</sup> (1928) gives an accurate description of the anaemia, which is the same anaemia as that described by Rowlands<sup>83</sup> (1924). Strauss<sup>88</sup> (1934) described 10 cases which responded to liver. Irving<sup>44</sup> (1935) did not see one case of 60 patients studied in regard to anaemia nor did Davis and Walker<sup>23</sup> (1934). It has been met with only infrequently in this country and is not of practical importance, but it definitely established that the blood picture though similar to that/



that of pernicious anaemia, is only temporary and due to a relative deficiency of the haematopoietic principle either as a result of defective intake of extrinsic factor or a relative deficiency of the intrinsic factor or to an increased demand for the haematopoietic principle in pregnancy (Davies<sup>21</sup>(1935)). There is no constant achylia gastrica and the condition recovers spontaneously after pregnancy and need not necessarily recur in succeeding pregnancies. This anaemia has to be distinguished from the true pernicious anaemia which may occur for the first time in pregnancy or may have existed before the start of the pregnancy. Although usually seen at a later age period, pernicious anaemia can occur in pregnancy as described, but it will require a continuation of treatment after the cessation of pregnancy.

The Haemolytic Anaemia is still more rarely seen and will not be discussed further except to say that it is distinct from the earlier "Haemolytic Anaemia" described by Rowlands and Allan which is really the anaemia just discussed above and not a true haemolysis.

We are now left with the group of Hypochromic Anaemias which for practical purposes constitutes all the anaemias met with in pregnancy in this country, after excluding those due to obvious causes e.g. haemorrhage, malignant disease, sepsis etc., which however may not be so obvious until sought for in any particular case.

Hypochromic/

Hypochromic Anaemia of Pregnancy. The title also serves as a definition for the anaemia.

Aetiology. 1. Iron. The primary defect is certainly an inadequacy of iron since there is a favourable response to the administration of iron in all the recorded cases in the literature (Mettier et al<sup>67</sup> (1933); Strauss<sup>88</sup> (1934); McGeorge<sup>61</sup> (1935); Bethell<sup>5</sup> (1936); Corrigan and Strauss<sup>17</sup> (1936); Smallwood<sup>84</sup> (1936); Boycott<sup>8</sup> (1936) and Fullerton<sup>33</sup> (1936)). The reason for this inadequacy is explained differently by different authors. An intake of iron below the required level must in many cases hold and this cannot be disputed. However, some authors seem rather to favour a relative deficiency resulting from increased demands in pregnancy, particularly by the foetus and perhaps by the mother also. (Strauss and Castle<sup>14</sup> (1933); Strauss<sup>88</sup> (1934); McGeorge<sup>61</sup> (1935) and Boycott<sup>8</sup> (1936)). It is certain that there is a big drain of iron from mother to foetus, particularly during the latter months (Coons<sup>16</sup> (1932)), but Bethell<sup>5</sup> (1936) showed that the total foetal drain of 350-450 mgms. of iron during pregnancy could be obtained from 1 litre of maternal blood. About one half of this is conserved owing to cessation of menstruation and the other half should be easily made up when we think of the rapidity of return to normal after the loss of 500 ccs. of blood by a donor. Further Davidson and Fullerton<sup>19</sup> (1938) showed/

showed that the loss of iron due to pregnancy, parturition and lactation was fully compensated for by the cessation of menstruation during this period and therefore the absolute need of an increased iron intake over the non-pregnant level is not upheld quantitatively. Further if no dietary iron was retained the haemoglobin level would only drop from 100% to 78% by the end of pregnancy (Fullerton<sup>33</sup> (1936)).

(a) Parity and Age.

If the needs of pregnancy in regard to iron are greater than those of the non-pregnant state then it seems reasonable to assume that frequent pregnancy would be an added strain on the Iron reserves and that anaemia in pregnancy would be more frequent in multiparae. The influence of age might be expected to act in like fashion since multiparae are likely to be more frequently found in later age groups. A distinction has therefore to be drawn between the true effect of age and that due to multiparity. Fullerton<sup>32</sup> (1936) showed that the incidence of anaemia in pregnancy increased up to the age of 44 years. The average haemoglobin for pregnant women with more than 5 pregnancies was 74.6% and the average age of the group 34.1 years, while the corresponding figures for women with less than three pregnancies was 79.2% and 23.7 years. That this difference is due to age and not to parity is shown when the same age groups are compared/



compared on the basis of parity. Those with more than three pregnancies showed a slight advantage as regards haemoglobin average over those with three or less pregnancies. Bland et al<sup>6</sup> (1930) stated that the effect of age and parity on the anaemia was practically nil. With this view McGeorge<sup>61</sup> (1935) and Boycott<sup>8</sup> (1936) also agree, while Linder and Massey<sup>53</sup> (1939) qualify their observations by saying that below 30 years, age seems to have no effect on the anaemia. This seems to agree with Fullerton's observations that anaemia advances in pregnancy up to 44 years of age. Linder and Massey, however, found a lower haemoglobin in multiparae, but this they attributed to greater menstrual loss and not to the increased strain, on the iron reserves, of frequent pregnancies per se. Lyon<sup>59</sup> (1929) and Galloway<sup>35</sup> (1929) both observed that frequent pregnancy had no direct relationship to the anaemia of pregnancy. The observation by Goodall and Gottlieb<sup>36</sup> (1936) that multiparae with spaced pregnancies show a more favourable haemoglobin level than those with rapidly succeeding pregnancies does not prove anything in respect of pregnancy per se, since other factors, e.g. Economic Status would appear to play a large part in the two groups.

All these observations point to one fact, that pregnancy throws no greatly increased strain upon the iron reserves of a woman, else the effect of parity would be clearly demonstrated by the increased frequency/

frequency of anaemia in multiparae. That there is an increased incidence of anaemia with advancing age is in correspondence with the findings in the non-pregnant and therefore the cause is likely to be the same, viz. paucity of iron intake in relation to the needs of adult life.

Regarding the increased maternal needs of tissue iron in pregnancy, it has been shown that this form of iron is not likely to be stored in an anaemic person i.e. the tissue iron storage is an optimal storage occurring only in those with full complement of haemoglobin. Therefore tissue iron requirements cannot be an important factor in the increased demands for iron in pregnancy (Hahn<sup>40</sup> (1937)).

Despite all that has been said in regard to the iron needs it must be admitted that in some cases the intake of iron is too low to satisfy the needs of either pregnancy or the non-pregnant stage and hence the importance of diet in pregnancy arises as an aetiological factor in the production of anaemia.

#### (b) Diet and Social Status.

An absorption of 2.5 mgms. of iron per diem from the diet is sufficient to meet the needs of normal menstruation and pregnancy, but this leaves no margin of safety to meet any added need (Davidson and Fullerton<sup>19</sup> (1938)) and many poor women may not retain this amount from diets which are inadequate in iron (Fullerton/

(Fullerton<sup>32</sup>(1936)). An investigation into the diets of pregnant women of differing social grade was carried out by McCance<sup>58</sup>(1938) and the results are the most accurate of those considered here since the diets were weighed and calculated over a period of one week, whereas most of the observers assessed the adequacy of the diets of their patients by questioning in regard to the frequency of intake of meat, fruit, vegetables, milk etc. The total calories of any group did not appear to be inadequate although below the recommended League of Nations' Standard (McCance<sup>58</sup>(1938) and Orr<sup>74</sup>(1940)). Castle and Strauss<sup>13</sup>(1932) also found that none of their 22 normal pregnant cases lacked in calories. Eggs, fruit, meat, fish and vegetables rose strikingly with rise in income (McCance<sup>58</sup>(1938)) and relative lack of these constitutes a relatively poorer diet in regard to protein and iron. The iron intake on the lowest income level given by McCance was 8 mgms. per diem and the highest 13 mgms. per diem. Orr's figures quoted by Drummond<sup>27</sup>(1940) for families under 8/- per head was 9.6 mgms. of iron per diem. The figures for daily intake in the diet in health are given as 15 mgms. for the non-pregnant and 20 mgms. for the pregnant (Drummond<sup>27</sup>(1940) and McCarrison<sup>60</sup>(1940)). It would appear therefore, as McCance points out that even the highest social grades are insufficiently nourished in pregnancy. However, /



However, it seems only fair to point out that Watson (1938), who found a low incidence of anaemia in pregnancy, states that the nutritional aspect of pregnancy anaemia is over-stressed. This indeed would appear to be the case when one remembers the small amount of iron which need be retained to make good the iron loss of pregnancy (Fullerton<sup>32</sup> (1936)). "The League Standard" and those quoted above must therefore be considered as optimal, since many, if not most, women remain healthy and do not attain these standards.

Diet and Economic Status vary the one directly with the other as is shown by McCance's figures. However, Bland et al<sup>7</sup> (1930) found such a high percentage of anaemia in hospital and in private patients that he concluded that environment was not altogether so important as made out to be. This may be accounted for in some instances by ignorance of correct diet among the well-to-do and fashions and vagaries in diet depending upon the pregnant state.

Most authors, however, agree that adequate diet is important for the prevention of anaemia in pregnancy (Strauss and Castle<sup>13</sup> (1932); Davies and Shelley<sup>22</sup> (1934); McGeorge<sup>61</sup> (1935); Fullerton<sup>32</sup> (1936); Adair et al<sup>2</sup> (1936) and Linder and Massey<sup>53</sup> (1939)). The confusion between true anaemia and hydraemia in pregnancy in the literature has already been pointed out and the confusion seems to cause difficulty in assessing the role/

role of diet in preventing anaemia. Irving<sup>44</sup> (1935) states that his 60 patients all had adequate diets but all showed anaemia requiring treatment. Closer study of his results show that the patients for the most part only manifested the hydraemia of pregnancy. Similarly Labate<sup>49</sup> (1939) in a large series of cases found that diet alone would not prevent anaemia, but the bulk of these probably only manifested an hydraemia. Boycott<sup>8</sup> (1936) made due allowance for hydraemia and found a relatively low incidence of anaemia in pregnancy. He concluded that there was no relationship between anaemia and social status but it seems probable that the type of patient studied offered little real contrast in social status or in diet.

The importance of purchasing power is to enable the patient to buy foods rich in iron and protein. Bethell<sup>5</sup> (1936) showed the importance of both these dietary constituents in relation to anaemia in pregnancy. The amount of iron and protein in the diet is usually in direct relation to the purchasing power (Fullerton<sup>32</sup> (1936)) and in the very poor studied by Davidson and Fullerton<sup>19</sup> in Aberdeen it is easy to understand the very high incidence of anaemia which is directly traceable to poor iron intake in the presence of increased needs. Other workers have not shown such a high incidence of anaemia (see Table VI on the Incidence of Anaemia) but none have worked among such a poor section of the community.

The/

The only source of iron normally is in the diet. The amount of iron and protein varies directly with purchasing power and having made allowance for the vagaries of intake and absorption consequent upon pregnancy, therefore it seems obvious that some difference in incidence of anaemia resulting from iron lack, would exist between those able to afford a good diet and those unable to obtain sufficient iron for their needs. The weight of evidence from the literature is in favour of this view.

The absolute amount of iron in the diet is not so important as the amount actually absorbed. It is to enable the minimum necessary amount of iron to be absorbed in all cases that diets rich in iron are recommended in pregnancy and not necessarily because the needs of pregnancy are much greater.

What factors then may arise in pregnancy to inhibit the absorption of iron?

#### (c) Gastric Function.

Achlorhydria and hypochlorhydria have frequently been noted in pregnancy and many authors have given this as a prime factor in the causation of anaemia in pregnancy. The occurrence of achlorhydria and hypochlorhydria are more frequent in the pregnant than in the non-pregnant, but this is a temporary state of affairs which normally recovers after delivery (Strauss and Castle<sup>12</sup> (1932); Davies and Shelley<sup>22</sup> (1934) and Goodall and Gottlieb<sup>36</sup> (1936)). Goodall and Gottlieb explained/



explained the presence of this reduction in gastric acidity by the fact that the foetal stomach contains no hydrochloric acid and that there is a drain of maternal hydrochloric acid for foetal needs.

The effect of hypoacidity on iron absorption has been shown by Mettler and Minot<sup>65</sup> (1929) and<sup>66</sup> (1931) and the subject fully discussed earlier. The question which arises now is its aetiological significance in the anaemia in pregnancy.

Dealing with Idiopathic Hypochromic Anaemia Davies<sup>20</sup> (1931) stressed the aetiological significance of achlorhydria and it seems reasonable that the same should apply to a hypochromic anaemia arising unnoticed in pregnancy. Davidson and Fullerton<sup>19</sup> (1938) however, showed that the achlorhydria was not an essential feature in the development of this type of anaemia. This will be more fully discussed later. For the present we must look for some evidence connecting gastric hypo-acidity with anaemia in pregnancy.

Strauss and Castle<sup>12</sup> (1932) studied 24 normal women in pregnancy and found that 75% did not secrete normal amounts of hydrochloric acid during pregnancy. Five out of the remaining six, showed a return of gastric acidity to higher levels after delivery. Three patients had post-histamine anacidity which did not recover after delivery. Therefore the bulk of the patients showed a reduction in gastric acidity in pregnancy. In another study in 1932, Strauss and Castle/

<sup>13</sup>Castle showed a reduction in haemoglobin, from the third month of pregnancy to the 10th day post-partum, of amounts varying directly in each group with the reduction in gastric acidity, the diets being correspondingly good in each of the three groups studied. A fourth group with hypoacidity and a poor diet showed a marked fall in haemoglobin, although not so great as the third group with anacidity and a good diet. The views of these workers may be summarised in the findings of Strauss<sup>88</sup> (1934) who stated that patients showing hypochromic anaemia in pregnancy have a reduced gastric acidity or a poor diet or both. Davies and Shelley<sup>22</sup> (1934) studied 51 normal pregnancies and found that six developed anaemia. The 45 non-anaemic showed a lowering in gastric acidity in pregnancy with a rise 5-6 days after delivery which was maximal about 2 months after delivery. The six cases which developed hypochromic anaemia had a poor diet in addition to the lowered gastric acidity and he also mentions other possible aetiological causes e.g. menorrhagia and pleural birth. Goodall and Gottlieb<sup>36</sup> (1936) give striking figures for the reduction in acidity in the three trimesters of pregnancy in 115 unselected cases. 85% of these recover in the puerperium although they are still subnormal after one week. In 12% of the cases the amount of hydrochloric acid after one week from the time of delivery is a mere trace and in the remaining 30% there is anacidity. These latter all showed/

showed multiple pregnancy in rapid succession and a low haemoglobin. This fact he seems to attribute to the effect of multiple pregnancy, which if not sufficiently spaced leads to an incomplete recovery of gastric acidity. The figures of Labate<sup>50</sup> (1939) for the gastric acidity of 56 patients, mostly in late pregnancy, do not show such a striking incidence of reduced gastric acidity. 75% showed normal acidity and only 9% anacidity after histamine. The haemoglobin and red cells seem to be reduced in proportion to the gastric acidity, but the author considers the cases too few in order to draw any definite relationship between the reduction of acidity and the occurrence of reduced haemoglobin. In a later study in 1940 of some of these 56 cases Labate showed that there was a return towards normal in red blood cells and haemoglobin before delivery. This recovery either before delivery or in the puerperium is noted by Strauss and Castle, Davies and Shelley and Gottlieb and Goodall and the fact seems clear that the reduction in haemoglobin is merely a manifestation of hydraemia and not of a true anaemia. The occurrence of reduced hydrochloric acid and reduced haemoglobin in pregnancy may therefore be purely co-incidental and no direct proof of the causal relationship of reduced acidity to anaemia is forthcoming. Indeed Davies and Shelley point out that the six cases developing anaemia, had other factors besides reduced gastric acidity which were/



were more likely to be the cause of anaemia. Experimental evidence in dogs is brought forward by Bussabarger et al<sup>11</sup> (1938) which the authors think may support the view that gastric achylia is a factor in human pregnancy anaemia. However, the comparison between 5 gastrectomised dogs studied in 15 pregnancies and 12 normal dogs in only 12 pregnancies would appear to leave uncontrolled other possible causes of anaemia in pregnancy, particularly diet in relation to its iron content.

Moore and Pillman-Williams<sup>69</sup> (1936) in their study of toxaemic cases of pregnancy were unable to find support for the views of Strauss and Castle and Davies and Shelley in regard to gastric acidity in pregnancy.

Reduction of acidity in pregnancy seems to be a common occurrence. We know that hydrochloric acid plays an important part in the utilisation of dietary iron but there is no definite proof that this reduced acidity has any direct influence upon the occurrence of hypochromic anaemia in pregnancy. The discussion of the role of achlorhydria in relation to hypochromic anaemia will be referred to again later and can be applied also to the pregnant state.

To Summarise the importance of iron as an aetiological factor it may be stated that it is the lack of iron which determines the existence of hypochromic anaemia in pregnancy. The demands for iron in pregnancy/

pregnancy are not greatly in excess of those in the non-pregnant state, but the availability and absorption of dietary iron are probably reduced in many cases of pregnancy anaemia due to the presence of reduced gastric acidity.

## 2. Older Views.

Of historical interest in the aetiology of pregnancy anaemia is the view put forward by Höfbauer and mentioned by Rowlands<sup>83</sup> (1924) in his discussion of the anaemias of pregnancy. Höfbauer believed that the chorionic syncytium produced a haemolysin in the early months of pregnancy which enabled the foetus to derive its iron supply from the blood of the mother. If this haemolysin was not neutralised in the later months by an anti-haemolysin formed by the mother, then the condition of haemolysis persisted and this led to the production of an anaemia. Our present knowledge of the time of onset of the microcytic anaemia of pregnancy would not fit into this view as will presently be seen.

Other older views mentioned by Bland et al<sup>7</sup> in a discussion of the anaemia of pregnancy were:-

(1) A simple dilution of the blood causing the appearance of anaemia (2) A relative insufficiency of blood for the increased vascular area and (3) An hydraemia of pregnancy which we have already discussed and which really includes the two simpler views (1) and (2) in this/

this paragraph. The condition of hydraemia cannot really be considered as an anaemia as was pointed out, but is a factor which must be considered in assessing anaemia in pregnancy and one which has given rise to much confusion in the literature.

### 3. Modern Views.

The two main views in regard to the anaemia of pregnancy both realise the fundamental lack of iron for its production, but differ in regard to the time of onset of this anaemia.

(a) The first view, held by Strauss and Castle<sup>14</sup> (1933) and Boycott<sup>8</sup> (1936) and mentioned by Sodeman<sup>85</sup> (1940) in a recent review of the subject, states that the anaemia arises de novo in pregnancy as a direct result of iron deficiency which is produced by (1) Inadequate intake governed by dietary defect and caprice and (2) Inadequate absorption due to gastric dysfunction and (3) Increased foetal demands.

(b) The second view, mentioned by Lyon<sup>57</sup> (1929), Bland et al<sup>7</sup> (1930), Mussey et al<sup>70</sup> (1932), Bethell<sup>5</sup> (1936), Adair et al<sup>2</sup> (1936) and Fullerton<sup>33</sup> (1936), states that the anaemia has pre-existed the pregnancy and has been accentuated and perhaps revealed for the first time by the hydraemia of pregnancy.

These two views may simply describe what is a known fact, namely that a pre-existing anaemia may continue into pregnancy or that a hypochromic anaemia may/



may be discovered for the first time in pregnancy, in which case the views are not difficult to reconcile; but the two views seem to differ fundamentally in that the first believes in the development of a hypochromic anaemia as a direct result of pregnancy, while the second does not believe this to be the case. Are these views absolutely either right or wrong or is it possible that the exponents of each view are right in the interpretation of the cases they have studied. Whitby and Britton in interpreting modern views cannot be dogmatic on this point but realise the possibility of both conditions existing. The development of a hypochromic anaemia de novo in pregnancy is therefore the only anaemia which can really be described as a true hypochromic anaemia of pregnancy. The existence of this anaemia as a clinical entity requires fuller consideration since serious criticism of this view has been brought forward by Fullerton<sup>33</sup> (1936). Before discussing his views it is necessary to obtain a picture of what is called the hypochromic anaemia arising as a result of pregnancy and the hypochromic anaemia which exists prior to pregnancy.

#### Clinical Pictures of the Anaemias.

These two conditions as described are haematologically the same, namely the anaemia is of the hypochromic, microcytic type with more marked reduction of haemoglobin than of red blood cells. The colour/

colour index is below unity and the mean corpuscular volume, mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration are all low. The leucocytes and the blood platelets are not affected. The icterus index is low and the van den Berg reaction is negative. There is no alteration in the bleeding or coagulation time. The disorder of the red blood cells arises at the normoblastic level in the marrow. Regarding the age of onset it has been clearly demonstrated (Davidson and Fullerton<sup>19</sup> (1938)) that both types occur in women during active sexual life usually between the ages of 20 and 45. Anaemia is not common before the age of 20 and recovers after the menopause. Witts<sup>95</sup> (1931) said that the Idiopathic Hypochromic Anaemia recovered spontaneously after the menopause and showed a maximum incidence between 40 and 50 in women. Almost all the cases of the Idiopathic Hypochromic Anaemia occur in women, and those few male cases who have shown the disease, have presented the essential aetiological factor of deficient iron utilisation.

The clinical picture of this idiopathic anaemia of iron deficiency in its severe forms, presents the usual anoxic symptoms common to any anaemia, weakness, lassitude, dyspnoea, palpitation, headaches and pallor. There is occasionally pre-cordial pain of an anginal type and sometimes oedema of the ankles. Due to defect of gastric secretion there are usually gastrointestinal/

gastro-intestinal symptoms, pain, anorexia, flatulence, fullness and even vomiting. Constipation is more common than diarrhoea. Other features may be associated, glossitis and atrophy of the tongue papillae, the Plummer-Vinson syndrome of dysphagia, Koilonychia, splenic enlargement and sometimes paraesthesiae.

In the severe cases of hypochromic anaemia in pregnancy described by Strauss<sup>88</sup> (1934), these anoxic symptoms are described together with achlorhydria and splenic enlargement in some cases. It is therefore apparent that little if any distinction can be drawn, from the clinical picture or the blood picture, between the hypochromic anaemias in pregnancy described by the two schools of thought.

Whitby and Britton realise this difficulty in trying to distinguish between the Idiopathic type manifesting itself in pregnancy and the type believed to be due solely to pregnancy and state that only, the age grouping and the less frequently associated achlorhydria in the pregnancy type and its complete recovery after delivery and iron therapy, help to distinguish the two types. In regard to age grouping we have already seen that both types occur in active sexual life in women and therefore there seems to be no helpful distinguishing feature here. The other two distinguishing features - achlorhydria and response to iron therapy - require fuller consideration.

1. Achlorhydria. Witts<sup>94</sup> (1930) who gave the first description of 50 cases of Idiopathic Hypochromic Anaemia/



Anaemia in this country stated that achlorhydria was a cardinal feature of his Simple Achlorhydric Anaemia. The gastric defect was present before and persisted after the cure of the anaemia. In 1931 he reports achlorhydria in 81% of his anaemic cases and that this persists after cure and is not the result of the anaemia. Discussing this subject fully Davidson and Fullerton<sup>19</sup> (1938) note the frequent association of gastric dysfunction with hypochromic anaemia called by them Chronic Nutritional Hypochromic Anaemia. 64.9% of their cases presented achlorhydria and another 14.6% showed hypochlorhydria. We have already mentioned the occurrence of achlorhydria in pregnancy and the anaemia associated with it and the remarks now being made can be applied to this condition also.

Davidson and Fullerton point out that achlorhydria occurs in normal people, also that a normal gastric acidity is sometimes associated with the type of anaemia under discussion. The only constant feature appears to be faulty nutrition in regard to iron. Further since achylia occurs before pernicious anaemia it might be expected that the achlorhydric anaemia would frequently be seen prior to the development of the pernicious anaemia. This is very infrequently seen in practice. (Davies<sup>20</sup> (1931) reported two cases which he described as transitional between pernicious anaemia and idiopathic hypochromic anaemia. One of these developed true pernicious anaemia later. He believed/

believed in degrees of gastric dysfunction and described four stages; the final being complete achylia associated with pernicious anaemia). Also Davidson and Fullerton show that patients with pernicious anaemia, who receive only a maintenance dose of liver for years, do not develop the anaemia of microcytic type when their diet is adequate.

Witts<sup>95</sup> (1931) believes that the achlorhydria is the result of a gastritis and that both conditions advance with age. The type of anaemia under discussion, he says is maximal at the end of the reproductive life (40-49 years) and tends to recover after the menopause. This is in agreement with the work of Davidson and Fullerton, but as these workers point out, it does not prove the chief importance of achlorhydric gastritis else the anaemia would not improve after the menopause.

The presence of achlorhydria before and after the anaemia is stressed by Witts. The fact that achlorhydria is seen before the onset of the anaemia proves nothing according to Davidson and Fullerton, since an equal number have normal acidity before the onset and many with achlorhydria do not develop the anaemia. Persistence of achlorhydria after cure cannot be said to be absolute since Davidson and Fullerton followed up 12 cases after cure and who had been well for at least one year and found that while 6 showed no change in/

in gastric acidity and 1 was actually worse, yet 5 showed an improvement and 2 of these 5 had a normal Gastric acidity.

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More recently Lundholm (1938 and 1939) studied this hypochromic anaemia and pointed out that the achlorhydria was neither the cause nor a necessary feature of the anaemia. It only occurred in 67% of the 306 cases. Also it was not a fixed condition, but seemed to be the result of alterations in the gastric mucosa consequent upon the anaemia. These changes in the stomach were either temporary or permanent depending upon the duration of the anaemia.

The development of this type of anaemia in patients - both male and female - who have had resection of the stomach and have developed achlorhydria as a result is sometimes adduced as evidence in favour of the causal role of achlorhydria. However, other factors such as faulty diet and rapidity of passage of food through the intestine, which results in faulty absorption, cannot be excluded as possible causes of the resulting anaemia.

Turning again to the statement of Whitby and Britton that the nature of the achlorhydria in the anaemia resulting from pregnancy is of a less severe and less constant nature than that occurring in the idiopathic type of the anaemia, we find that the above evidence does not lend support to this view. Indeed it/



it cannot even be said that achlorhydria is essential to the production of the idiopathic type and is certainly not present in 100 per cent of cases. Some other aetiological factor has to be sought and all the evidence points to iron shortage, either absolute or relative to the demands, whether in pregnancy or the non-pregnant stage. The importance of the hydrochloric acid in the stomach is probably in relation to the availability and absorption of the dietary iron.

(Davidson and Fullerton<sup>19</sup> (1938) and Discussion on Iron Metabolism in the mother). Beebe and Wintrobe<sup>4</sup> (1933) were unable to draw any conclusions regarding the role of normal gastric function in iron absorption, while Lundholm found that in a population taking an average of 9 mgms. of dietary iron daily, the individual cases gave no sure proof of the correlation between dietary iron and anaemia (cf. Khan<sup>47</sup> (1941)). Difficulty in absorption of iron is the primary factor according to Lundholm and this he believes to be an inborn error of metabolism. Whether the hereditary factor be correct or no, the difficulty in iron absorption stressed by Lundholm seems to correspond with the views of Davidson and Fullerton on availability of iron, rather than the absolute amount in the diet, as being of importance.

Achlorhydria then, as a distinguishing feature in the two types of anaemia under discussion does not seem to be upheld from the evidence, in the literature, since the achlorhydria associated with the Idiopathic type/

type of the anaemia is no more constant than that occurring in the anaemia of pregnancy.

2. Iron Response. None doubt the curative effect of inorganic iron in anaemia arising apparently de novo in pregnancy and the idiopathic hypochromic anaemia of adult women. Whitby and Britton endeavour to make the response to iron in each condition a distinguishing feature between the two anaemias. The distinction they say is the fact that most cases arising in pregnancy can discontinue treatment afterwards whereas the true idiopathic cases require to continue treatment for a longer period. This might in part be explained by a return of the hypoacidity or anacidity of pregnancy to more normal levels after delivery, but the assumption is that the difference arises owing to the lessened demands for iron after the termination of pregnancy. The amount to which the iron demands are increased in pregnancy and lactation has been fully discussed in considering the work of Fullerton<sup>33</sup> (1936) and Bethell<sup>5</sup> (1936) and these were found to be insufficient to account for the severe anaemias met with in pregnancy. Therefore this reduction in the amount of iron required by the non-pregnant is so small as compared to the pregnant that it cannot fully explain the recovery of many cases after pregnancy and the ability of these cases to stop iron therapy.

Some other explanation must be sought and it seems probable that the confusion in many instances over/

over hydraemia and anaemia in pregnancy accounts for some cases. Again the diet in some may become more adequate after recovery from the pregnancy. Davidson and Fullerton<sup>19</sup> (1938) referred to the tendency of cases of the Idiopathic anaemia to relapse after discontinuing treatment and believed that the reason was the continuance of a poor diet. The cases of anaemia arising in pregnancy which recover completely after cessation of iron therapy and pregnancy, have probably continued to take adequate diet which has prevented relapse.

It is therefore apparent that any distinction, between hypochromic anaemia resulting from pregnancy and hypochromic anaemia in pregnancy of the idiopathic type, is artificial. Fullerton<sup>32</sup> (1936) aptly points out that the proof of the anaemia arising de novo in pregnancy would be a fall in the colour index from normal to subnormal during the period of gestation. No proof of this is forthcoming in the literature and we are therefore unable to say that the anaemia has not antedated the pregnancy. Whitby and Britton in introducing the hypochromic anaemia of pregnancy state that we must not lose sight of the fact that pregnancy frequently brings about the first recognition of an idiopathic hypochromic anaemia. This fact cannot be doubted and fits into the views expressed by Fullerton, since at some period the anaemia must first be discovered/



discovered and pregnancy is one of the periods in a woman's life when she consults a doctor, when otherwise she might never have done so for what she might consider the trivial complaint of tiredness.

One might attempt a compromise between the views of Fullerton and Strauss, as representing the two opposing schools of thought. Bethell in his quantitative results for the period of gestation and the immediate puerperium calculated that the iron saved by cessation of menstruation for nine months did not fully compensate for the iron requirements of pregnancy and labour. The difference he believed could be easily made up and could not account for the severe anaemias of pregnancy. However, if we assume that the woman enters pregnancy with a low normal haemoglobin and a diet low in iron, then this small extra amount of iron required in pregnancy could tip the scales in favour of an hypochromic anaemia developing in pregnancy.

Most cases of hypochromic anaemia manifest themselves early in pregnancy which would be a fact in favour of a pre-existing anaemia, since only towards the end of pregnancy is there a greatly increased foetal demand and the complete failure of iron intake could only reduce the haemoglobin by a slight amount in the early months of pregnancy. (Fullerton<sup>32</sup> (1936)).

It must be admitted that in the absence of direct proof of the development of an anaemia due to pregnancy per/

per se, the weight of evidence is in favour of a pre-existing hypochromic anaemia of nutritional origin or at any rate an anaemic tendency, which pregnancy and a continued low iron intake and assimilation, affect adversely causing the appearance of hypochromic anaemia, it may be for the first time, in pregnancy. It may be recalled that in discussing the anaemic cases in this series of 104 pregnancies, there were two groups of cases - the one treated by iron and the other untreated. The former seemed to show an early onset of the anaemia, which the latter group may also have shown but of which there is no proof. It appeared that the untreated group showed a later onset of the anaemia, when the iron drain was most severe, but unfortunately this late onset cannot be definitely proved and therefore there are insufficient grounds for any distinction being drawn between the two groups. Further there seems no justification for considering the possibility of two types of anaemia existing, as both are haematologically similar, occur in the same age group in women, are both caused by a defect in available iron, either relative or absolute, which defect is closely linked with gastric function, but which is not absolutely dependent upon achlorhydria as a primary aetiological factor. The prognosis of each is good if recovery is ensured by adequate iron therapy and the diet thereafter suitably adjusted to ensure an adequate iron intake.

#### Summary/

Summary. We may summarise these remarks by stating that the hypochromic anaemia met with in adult women up to the menopause either in pregnancy or the non-pregnant state is one and the same disease being manifest sometimes before, sometimes during and sometimes after pregnancy. The phases of a woman's active sexual life seems to be merely co-incidental to the onset of the anaemia. The true aetiological factor is lack of iron for haemoglobin formation, governed by supply and demand and the ability of the individual to absorb iron. The role of the gastric acidity in regard to iron availability and absorption is in doubt, but it is clear that the presence of achlorhydria is not an essential to the development of the anaemia and may even itself be dependent on the blood condition.

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SUMMARY.

Following the Introduction to this study of 104 pregnant women, in relation to the blood condition of pregnancy and the first six weeks of the puerperium, the method employed in the investigation is fully described. The Sahli Haemoglobinometer was described and standardised to the method used, and the alteration in its use in the case of foetal haemoglobin estimations was discussed. The cases were then divided into groups for the purpose of the investigation.

A Normal Haemoglobin standard for the non-pregnant was established both from the relevant literature and from personal observations and these results were found to be closely related and to lie in the region of 14 Gms. of haemoglobin per 100 ccs. of whole blood for normal healthy women of child-bearing age. (Tables I and II).

Proceeding from this standard it was possible by comparing the literature with one's own results of normal pregnant women to establish normal haemoglobin levels for pregnancy. First of all the variation in level during the three trimesters of pregnancy was considered and found to be related to the condition of hydraemia. Secondly a mean average haemoglobin for the whole of pregnancy was established and from this a lower limit of normality for the haemoglobin level in pregnancy was adopted. This figure was seen to/

to be in the region of 10 Gms. per 100 ccs. and is similar to what we calculated from the relevant facts regarding the non-pregnant and the alteration in blood volume as a result of pregnancy. (Table III and Table IV with Graph I).

Having established an anaemia level for the haemoglobin in pregnancy it was then possible to discuss more fully the normal blood changes in pregnancy and the puerperium. This was done by a consideration of the literature and the recording of personal results. Particular stress attached to the hydraemia of pregnancy and the gradual return of this state to normal in late pregnancy and the puerperium (Table V and Graph II).

We were then in a position to discuss the incidence of anaemia in pregnancy. (Table VI) A study of previous work showed the presence of some confusion between anaemia and hydraemia and an endeavour was made to correct these mis-interpretations as they affected the incidence of anaemia in pregnancy. No absolute figure could be given for the incidence of anaemia in pregnancy, but from one's own results, on the basis already established for anaemia, the incidence was about 10%. (Table VII and Graphs III & IV).

The Effect of Iron Therapy was then fully considered. Again confusion was thought to be evident in the recorded results of some and by careful selection of cases it was shown that in this series there was/

was no significant benefit to the patient and her child, either in pregnancy or the puerperium, by the administration of iron in pregnancy or the puerperium or in both. (Table X and Graphs V and VI and Tables XVIII-XX with Graphs XV-XVIII). This argument was fully developed from the cases in this series and graphs, of initial haemoglobin levels and haemoglobin levels after varying periods of treatment, were presented to add confirmation to this thesis. (Tables XI-XVII and Graphs VII-XIII). There was no doubt whatsoever in regard to the efficacy of iron therapy in anaemic cases in the antenatal or post-natal periods. This was illustrated from the literature and from personal observations. (Graph XIV and Graphs XIX and XX with Tables XXI and XXII). Indeed it even seemed in one group that iron given ante-natally had benefited the treated cases with <sup>excessive</sup> parturient blood loss, when compared to similar women untreated in pregnancy. (Tables XXIII and XXIV with Graphs XXI and XXII).

Continuing the study of iron therapy in pregnancy, we considered the effects, if any, of iron therapy upon the occurrence of certain abnormalities of pregnancy labour and the puerperium (Table VII). The effect of iron therapy appeared to be nil except in so far as it corrected any anaemia, which itself only appeared to give rise to an increased susceptibility towards septic infection in the mother, besides any symptoms/



symptoms of the anaemia per se. This study was augmented from a consideration of the relevant literature.

The results of this clinical study having been recorded in the preceding sections and deductions made in the light of the findings and the conclusions found in the literature, a discussion of the problem of anaemia of pregnancy was given. This was prefaced by a consideration of the Maternal and the Foetal Iron Metabolisms. The anaemias of pregnancy were classified and it was shown that the only one of practical importance in this country is the Hypochromic type.

The aetiology of this anaemia was discussed and it was shown that iron lack was the fundamental factor in its production. Certain factors likely to have a bearing on this iron shortage were discussed, viz. Age and Parity, Economic Status and Diet and Gastric Function. Certain older historical views regarding the aetiology were mentioned as being unimportant in the light of modern knowledge.

The question of there being two distinct hypochromic anaemias in pregnancy was fully considered and the conclusion reached that, in view of the identical clinical pictures and the fundamental iron lack in each, there was no reason to draw any distinction. The hypochromic anaemia of pregnancy was therefore identified as the Nutritional Hypochromic Anaemia found in adult women of child-bearing age.

CONCLUSIONS.

One hundred and four cases of pregnancy, described and considered in the light of previous work, have been presented. It has been shown that the majority of the cases could be considered normal in regard to the blood picture which they presented and these normal cases have been used to demonstrate the normal behaviour of the blood in pregnancy and the puerperium.

The striking feature in pregnancy is the occurrence of the hydraemia, which seems to have been the cause of much confusion in the literature, particularly when the results of iron administration have been considered. We have endeavoured to show that this reduction in the haemoglobin during the second and most of the third trimesters of pregnancy is physiological and not influenced significantly by the administration of iron during pregnancy. The consideration of the iron treated groups bore this out, while a study of the initial haemoglobin levels at various stages in pregnancy, and the haemoglobin levels at various stages in groups treated for periods up to 20 weeks, also confirmed this since the general curve of the haemoglobin level during pregnancy was comparable/

comparable in each group studied. The period of gestation is therefore the chief factor in determining the haemoglobin level found in any normal case. In the puerperium, the normal behaviour of the blood was considered, and the treated groups, as previously described, were shown to hold no advantage over the normal.

The thesis therefore seems to be maintained, that there is no advantage to be derived from iron administration in pregnancy, the puerperium or both, either to the mother or child if the former be not anaemic.

It was shown that the incidence of anaemia in pregnancy, exclusive of secondary anaemia, only amounted to little over 10% and therefore it seems reasonable to say, that routine iron therapy is not justified in order to benefit this minority. The anaemic cases can easily be found by routine haemoglobin estimation during ante-natal examinations.

The benefit of iron to anaemic cases, of the type found in this series, is undoubted whether the anaemia occurs in pregnancy or the puerperium and whether of the primary nutritional or the secondary type.

The slight advantage in the puerperal recovery of the blood from the administration of iron in pregnancy, to those suffering from an iron lack as a result of haemorrhage at delivery, has been shown, but the numbers/



numbers involved are so small as not to justify routine iron therapy.

The onset of complications of pregnancy, labour and the puerperium was not found to be related in any way to iron therapy in normal cases and therefore this also does not justify routine iron therapy. Anaemic cases are probably more prone to septic infection but not to the other complications of pregnancy, labour or the puerperium; iron therapy by restoring the blood level to normal increases the resistance of these cases to infection.

Since this study was undertaken from a practical, clinical standpoint, it may be said that the point of chief interest is the need for routine haemoglobin estimation in pregnancy in order to find out and treat any anaemic cases. This seems more scientific and sensible than the routine administration of iron in pregnancy. The ideal, of course, would be the prevention of anaemia in adult women by proper dietary, which in addition would ensure an adequate intake of other minerals and vitamins no less important than iron. The attainment of this goal is not yet in sight and until this ideal is reached it is better that we should make good any deficiency known to exist, either from a study of the diet and its correction where possible or from clinical observation of any deficiency and its treatment as exemplified/

exemplified by this study of anaemia, rather than administering drugs routinely to many who have no need of them.

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